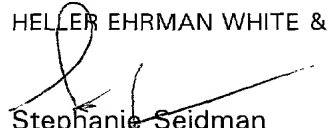


09/05/00

09-07-00

B-X SEP A

TRANSMITTAL OF UTILITY APPLICATION UNDER 37 C.F.R. §1.53		Attorney Docket No.	18021-2919B
		First named inventor	Paul Sternberg
		Express mail label #	EL576845655US
		Date of mailing	September 5, 2000
Application Elements		Accompanying Application Papers	
1. <input checked="" type="checkbox"/> Fee Transmittal Form 2. <input checked="" type="checkbox"/> Specification containing <u>69</u> pages (including claims and Abstract) and a Sequence Listing (62 pages). a. Title: POLYCYSTIC KIDNEY DISEASE GENE HOMOLOGS REQUIRED FOR MALE MATING BEHAVIOR IN NEMATODES AND ASSAYS BASED THEREON b. Number of claims: <u>63</u> 3. <input checked="" type="checkbox"/> <u>7</u> sheets of drawings with <u>4</u> Figs. 4. <input checked="" type="checkbox"/> Copy of Declaration from parent application 5. <input checked="" type="checkbox"/> Sequence Listing (62 pages) <input checked="" type="checkbox"/> Paper copy (identical to computer copy) <input checked="" type="checkbox"/> Computer readable copy <input type="checkbox"/> Verified statement		6. <input type="checkbox"/> Copy of assignment from prior 7. <input checked="" type="checkbox"/> Copy of Small Entity Statement filed in priority application 8. <input type="checkbox"/> Preliminary Amendment 9. <input checked="" type="checkbox"/> Return Receipt Postcard	
		SIGNATURE OF ATTORNEY/AGENT HELLER EHRMAN WHITE & McAULIFFE LLP  Stephanie Seidman Registration Number: 33,779	
[X] This application is a divisional of U.S. application Serial No. 09/479,467, filed January 6, 2000 is claimed. Benefit of priority under 35 U.S.C. §119(e) to U.S. Provisional Application Serial No. 60/115,127, filed January 6, 1999 is also claimed. The subject matter of each of these applications is incorporated by reference in its entirety.			
CORRESPONDENCE ADDRESS			
NAME	Stephanie Seidman Registration No. 33,779 Heller Ehrman White & McAuliffe LLP		
Address	4250 Executive Square, 7th Floor, La Jolla, CA 92037		
	Telephone: 858.450-8400	Facsimile: 858.587-5360	

09/05/00

FEE TRANSMITTAL ACCOMPANYING UTILITY APPLICATION UNDER 37 C.F.R. §1.53	Attorney Docket No.	18021-2919B
	First named inventor	Paul Sternberg
	Express mail label #	EL576845655US
	Date of mailing	September 5, 2000

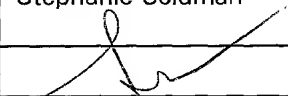
FEE CALCULATION FOR CLAIMS AS AMENDED

a)	Basic Fee		\$ 690.00
b)	Independent Claims $\frac{15}{3} = \frac{12}{3}$	$\times \$ 78.00$	\$ 936.00
c)	Total Claims $\frac{63}{20} = \frac{43}{20}$	$\times \$ 18.00$	\$ 774.00
d)	Fee for Multiple Dependent Claims -	\$230.00	\$ 0.00
TOTAL FILING FEE			\$ 2400.00

[X] Statement(s) of Status as Small Entity
reducing Fee by one-half to \$1200.00

[X] A check in the amount of \$1200.00 to cover the fee for filing the application.

[X] The Commissioner is hereby authorized to charge any fees that may be required in this application during its entire pendency, or credit any overpayment, to Deposit Account No. 50-1213. If proper payment is not enclosed, such as a check in the wrong amount, unsigned, post-dated, otherwise improper or informal, or absent, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 50-1213 during the entire pendency of this application. This sheet is filed in duplicate.

CORRESPONDENCE ADDRESS			
NAME	Stephanie Seidman Registration No. 33,779 Heller Ehrman White & McAuliffe LLP		
Address	4250 Executive Square, 7th Floor, La Jolla, CA 92037		
	Telephone: 858.450.8400	Facsimile: 858.587-5360	
Submitted by:			
Typed or printed name	Stephanie Seidman		Reg. Number 33,779
Signature		Date 09/05/00	Deposit Account 50-1213

00900900

TOLNEY DOCKET NO. 06618/391001/CIT2919

Applicant or Patents: Paul W. Sternberg et al.

Serial or Patent No.:

Filed or Issued:

For:

1/6/99

CAENORHABDITIS ELEGANS STRAINS PERTURBED IN POLYCYSTIN FUNCTION

VERIFIED STATEMENT (DECLARATION) CLAIMING SMALL ENTITY STATUS
(37 CFR 1.9(f) and 1.27(d)) - NONPROFIT ORGANIZATION

I hereby declare that I am an official empowered to act on behalf of the nonprofit organization identified below:

Name of Organization: California Institute of Technology
Address of Organization: 1200 East California Blvd.
Type of Organization:

- ☒ UNIVERSITY OR OTHER INSTITUTION OF HIGHER EDUCATION
☐ TAX EXEMPT UNDER INTERNAL REVENUE SERVICE CODE (26 USC 501(a) and 501(c)(3))
☐ NONPROFIT SCIENTIFIC OR EDUCATIONAL UNDER STATUTE OF STATE OF THE UNITED STATES OF AMERICA
 (NAME OF STATE:)
 (CITATION OF STATUTE:)
☐ WOULD QUALIFY AS TAX EXEMPT UNDER INTERNAL REVENUE SERVICE CODE (26 USC 501(a) and 501(c)(3)) IF LOCATED IN THE UNITED STATES OF AMERICA
☐ WOULD QUALIFY AS NONPROFIT SCIENTIFIC OR EDUCATIONAL UNDER STATUTE OF STATE OF THE UNITED STATES OF AMERICA IF LOCATED IN THE UNITED STATES OF AMERICA
 (NAME OF STATE:)
 (CITATION OF STATUTE:)

I hereby declare that the nonprofit organization identified above qualifies as a nonprofit organization as defined in 37 CFR 1.9(e) for purposes of paying reduced fees under section 41(a) and (b) of Title 35, United States Code with regard to the invention entitled CAENORHABDITIS ELEGANS STRAINS PERTURBED IN POLYCYSTIN FUNCTION by inventor(s) PAUL W. STERNBERG AND MAUREEN M. BARR described in

- ☒ the specification filed herewith.
☐ application serial no. , filed .
☐ patent no. , issued .

I hereby declare that rights under contract or law have been conveyed to and remain with the nonprofit organization with regard to the above identified invention.

If the rights held by the nonprofit organization are not exclusive, each individual, concern or organization having rights to the invention is listed below and no rights to the invention are held by any person, other than the inventor, who could not qualify as a small business concern under 37 CFR 1.9(c) or by any concern which would not qualify as a small business concern under 37 CFR 1.9(d) or a nonprofit organization under 37 CFR 1.9(e).

NOTE: Separate verified statements are required from each named person, concern or organization having rights to the invention averring to their status as small entities. (37 CFR 1.27)

Full Name: _____

Address: _____

☐ INDIVIDUAL ☐ SMALL BUSINESS CONCERN ☒ NONPROFIT ORGANIZATION

I acknowledge the duty to file, in this application or patent, notification of any change in status resulting in loss of entitlement to small entity status when any new rule 53 application is filed or prior to paying, or at the time of paying, the earliest of the issue fee or any maintenance fee due after the date on which status as a small entity is no longer appropriate. (37 CFR 1.28(b))

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of this application, any patent issuing thereon, or any patent to which this verified statement is directed.

Name: Adam CochranTitle: The Intellectual Property CounselAddress: 1200 East California Blvd., Pasadena, CA 91125Signature: Date: January 6, 1999

005060-0955160-000000

**POLYCYSTIC KIDNEY DISEASE GENE HOMOLOGS REQUIRED FOR MALE
MATING BEHAVIOR IN NEMATODES AND ASSAYS BASED THEREON
RELATED APPLICATIONS**

This application is a divisional of U.S. application Serial No.

- 5 09/479,467, filed January 6, 2000, to Paul W. Sternberg and Maureen M. Barr, and entitled "POLYCYSTIC KIDNEY DISEASE GENE HOMOLOGS REQUIRED FOR MALE MATING BEHAVIOR IN NEMATODES AND ASSAYS BASED THEREON". Benefit of priority under 35 U.S.C. §119(e) to U.S. Provisional Application Serial No. 60/115,127, entitled
- 10 "*CAENORHABDITIS ELEGANS* STRAINS PERTURBED IN POLYCYSTIN FUNCTION" to Paul W. Sternberg and Maureen M. Barr, filed January 6, 1999, is also claimed herein. The subject matter of each of U.S. Provisional Application Serial No. 60/115,127 and U.S. application Serial No. 09/479,467 is incorporated in its entirety by reference.

15 FIELD OF INVENTION

- Systems and assays for identification of compounds that can be used to treat polycystic kidney disease (PKD) are provided. Nematode orthologs of genes involved in PKD are identified and associated with mating behaviors. In particular, nematodes, such as *Caenorhabditis*
- 20 *elegans*, that express mutant and wild-type orthologs of human genes involved in this disease, are used to study the functions of the proteins encoded by the genes, to screen for other genes involved in the disease, to identify mutations involved in the disease, and to screen for drugs that affect PKD. Hence an animal model is provided that permits study of the
- 25 etiology of polycystic kidney disease and provides a tool to identify the genes and factors involved in the disease pathway, and to identify compounds that may be used to treat or alter the disease progression, lessen its severity or ameliorate symptoms.

BACKGROUND

Polycystic Kidney Diseases

Polycystic kidney diseases (PKD) are a group of disorders characterized by the presence of a large number of fluid-filled cysts throughout grossly enlarged kidneys (Gabow *et al.* (1992) *Diseases of the Kidney*, Schrier *et al.* eds.). In humans, PKDs can be inherited in autosomal dominant (ADPKD) or autosomal recessive (ARPKD) forms. ADPKD is the more common form and is the most common, dominantly-inherited kidney disease in humans, occurring at a frequency of about 1 in 800. ARPKD occurs at a frequency of about 1 in 10,000.

ADPKD is the most common single-gene disorder leading to kidney failure (see, Emmons *et al.* (1999) *Nature* 401:339-340). Since ADPKD is inherited as an autosomal dominant disorder, children of affected parents have a one in two chance of inheriting the disease. Although the kidney is the most severely affected organ, the disease is systemic and affects the liver, pancreas cardiovascular system and cerebro-vascular system. The major manifestation of the disorder is the progressive cystic dilation of renal tubules (Gabow (1990) *Am. J. Kidney Dis.* 16:403-413), leading to renal failure in half of affected individuals by age 50. Microdissection, histochemical and immunologic studies show that cysts in ARPKD kidneys arise from focal dilations of medullary collecting ducts (McDonald (1991) *Semin. Nephrol.* 11:632-642). Although end-stage renal failure usually supervenes in middle age (ADPKD is sometimes called adult polycystic kidney disease), children may occasionally have severe renal cystic disease.

ADPKD-associated renal cysts may enlarge to contain several liters of fluid and the kidneys usually enlarge progressively causing pain. Other abnormalities such as hematuria, renal and urinary infection, renal tumors, salt and water imbalance and hypertension frequently result from the renal defect. Cystic abnormalities in other organs, including the liver, pancreas, spleen and ovaries are commonly found in ADPKD. Massive

liver enlargement can causes portal hypertension and hepatic failure. Cardiac valve abnormalities and an increased frequency of subarachnoid and other intracranial hemorrhage have also been observed in ADPKD.

- Progressive renal failure causes death in many ADPKD patients and
- 5 dialysis and transplantation are frequently required to maintain life in these patients.

- Numerous biochemical abnormalities associated with this disease also are observed. These include defects in protein sorting, the distribution of cell membrane markers within renal epithelial cells,
- 10 extracellular matrix, ion transport, epithelial cell turnover, and epithelial cell proliferation.

- Three distinct loci have been shown to cause phenotypically indistinct forms of the AKPKD in humans. These include polycystin-1 (PKD1) on chromosome 16, polycystin-2 (PKD2) on chromosome 4, and
- 15 polycystin-3 (PKD3) (see, *e.g.*, Reeders *et al.* (1985) *Nature* 317:542-544; Kimberling *et al.* (1993) *Genomics* 18:467-472; Daoust *et al.* (1995) *Genomics*, 25:733-736). The ARPKD mutation is on human chromosome 6 (Zerres *et al.* (1993) *Nature Genet.* 7:429-432). Two proteins polycystin-1 (PKD1) and polycystin-2 (PKD2) are defective in
- 20 human autosomal dominant polycystic kidney disease.

- Mutations in either PKD1 or PKD2 cause almost indistinguishable clinical symptoms. Mutations in PKD1 or PKD2 account for 95% of autosomal dominant polycystic disease (Torres *et al.* (1998) *Current Opinion in Nephrology and Hypertension* 7:159-169) with greater than
- 25 85-90% of disease incidence being due to mutations in PKD1.

- The human PKD1 protein is an approximately 4,300 amino-acid integral-membrane glycoprotein with a large amino-terminal extracellular domain and a small, carboxy-terminal cytoplasmic tail. The human PKD1 gene (see, *e.g.*, U.S. Patent No. 5,891,628), including the complete
- 30 nucleotide sequence of the gene's coding region (se SEQ ID No. 1) and encoded amino acid sequence, is known (see, SEQ ID No. 2). The

predicted structure of the domains suggested that it is involved in cell-cell interactions or in interactions with the extracellular matrix. The PKD2 protein has similarities to PKD1, but its topology and domain structure suggest that it might act as a subunit of a cation channel. These proteins have been shown to interact directly (Mochizuki *et al.* (1996) *Science* 272:1339-1342, Qian (1997) *Nature Genetics* 16:179-183).

Although these genes have been implicated in the disorders their role in its etiology is not established. In addition, while studies of kidneys from ADPKD patients exhibit a number of different biochemical, structural and physiological abnormalities, the disorder's underlying causative biochemical defect is not known. Hence the molecular mechanisms leading to cyst enlargement and progressive loss of renal function in the PKDs are not understood. Presently there are no cures or effective treatments, other than palliative treatments, for these diseases. Hence there is a need to understand the underlying biochemistry and physiology of the ADPKD and to provide treatments.

Therefore, it is an object herein to provide a means to identify the underlying biochemistry and genetics of these diseases and to provide a means to identify compounds for use in treatment of these diseases.

20 SUMMARY

Isolated genes, cDNA and encoded proteins from nematodes that participate in a pathway leading to an observable phenotype are provided. In particular, it is shown herein, that a mutation in *C. elegans*, which gives rise to males that are defective in certain aspects of mating behavior, lies in a gene designed herein *lov-1* (location of vulva), and that this gene is an ortholog of the mammalian, particularly human, PKD1 gene. A mutation in a gene designated *pkd-2* herein also gives rise to these behaviors. This gene is shown to be an ortholog of the mammalian, including human, PKD2 gene.

30 The expression pattern of *lov-1* and *pkd-2* was studied and it was found that promoter sequences of both genes cause reporter genes to be

expressed in the rays and the hook sensory neurons required for 'response' and vulva location. Thus showing that the LOV-1 and PKD-2 proteins are involved in chemosensory or mechanosensory signal transduction in sensory neurons.

- 5 Hence genes that are components of a pathway in nematodes are provided and are shown to be linked to observable behaviors. Each of the encoded proteins, LOV-1 and PKD-2 are components in a pathway, which appears to be a signal transduction pathway, that leads to the observed phenotype. The genes from the nematode *Caenorhabditis elegans* are
10 exemplified herein.

- The pathway is shown to be homologous to the pathway in which the human polycystins, PKD1 and PKD2, participate. In particular, it is shown herein, that a mutation in nematodes, which gives rise to males that are defective in mating behavior, lies in a gene designated herein
15 *lov-1* (location of vulva). This gene, *lov-1*, is shown herein to be required for two male sensory behaviors, 'response' and 'location of vulva' (Lov).

- A second gene, designated *pkd-2*, that affects this behavior in a similar manner is also identified and provided herein. The encoded proteins are also provided. The gene, cDNA, and encoded protein is also
20 provided. In an exemplary embodiment, the *C. elegans* genome sequence was used to isolate *pkd-2*. This gene is a nematode ortholog of the mammalian, particularly human PKD2 gene. Strains that contain knock-out mutants of this gene also exhibit the defective mating behaviors.

- In an exemplary embodiment, provided herein are the *C. elegans*
25 genes, designated *lov-1* and *pkd-2*. SEQ ID No. 3 sets forth the complement (*i.e.*, the non-coding strand) of the *lov-1* gene from *C. elegans*. SEQ ID No. 4 sets forth the sequence of amino acids of the protein (N-terminus to C-terminus)). SEQ ID No. 5 sets forth the complement (*i.e.*, the non-coding strand) of the *C. elegans pkd-2* gene
30 from *C. elegans*. SEQ ID No. 6 sets forth the encoded sequence of amino acids.

Also provided are the mutants of the genes, *lov-1*, and *pkd-2* and the resulting mutant encoded proteins. Nucleic acid molecules encoding mutants of these genes are also provided. For example, deletion mutants of these genes, particularly deletion mutants that substantially or

- 5 completely knock-out gene product function, are provided. Thus, nucleic acid molecules containing deletions of each of these genes and deletion mutants that alter the phenotype of nematodes, such as *C. elegans*, that contain these mutant genes are also provided. Constructs, vectors, plasmids and strains containing each of the nucleic molecules are also
- 10 provided. Also provided are strains defective in these genes.

Also provided are strains containing the mutant nucleic acids. Strains that manifest the defective male sensory behaviors are also provided herein. Constructs containing the genes, vectors containing the constructs, cells containing the vectors and transgenic *C. elegans*.

- 15 Assays that use these strains of *C. elegans* are also provided.

- As noted, it is shown herein that these genes are human homologs of the human genes that encode polycystins, proteins polycystin-1 (PKD1) and polycystin-2 (PKD2), which are defective in human autosomal dominant polycystic kidney disease. Hence, the genes and nematode
- 20 strains provide model systems for studying this pathway, identifying additional components of the pathway, and for use in drug screening assays to identify compounds affect the pathway and/or compounds that serve as leads for development of drugs for treatment of polycystic kidney disease.

- 25 Each gene is shown to affect two sensory behaviors in *C. elegans*. One behavior designated "Response" and refers to the response of males to hermaphrodites; and the other behavior, designated "Lov" refers to location of the vulva by the male. Strains that are defective in either or both of these genes are also provided. In particular deletion mutants are
- 30 provided.

By correlating the phenotypic behaviors with wild-type or defects in these genes, nematodes, such as *C. elegans*, can be used to identify other genes involved in this pathway and also means for direct screening for lead candidate compounds for drugs for treatment of PKD. Identification of additional genes necessary for PKD function can provide additional diagnostic tools for PKD. Hence, provided herein are mutant strains of *C. elegans* and assays that use the strains.

Also provided herein are assays that employ the constructs, vectors, plasmids and strains containing each of the nucleic molecules are also provided. In particular, in one type of assays wild-type nematodes are mutagenized or treated with a test compound, and those that exhibit a change in behavior are identified.

In other types of assays, nematodes that are defective in LOV and/or Response are mutagenized or treated with a compound, and those that exhibit a change in behavior are identified. Test compounds or mutations responsible for the change in behavior are identified. Such compounds are candidates for treatment of PKDs.

Among these methods are those that involved contacting a nematode that exhibits normal mating behavior with a test compound; and selecting compounds that result in altered mating behavior, wherein the altered mating behavior comprises alteration in the behavior involving location of vulva and/or response to contact with the hermaphrodite.

Also provided are methods for identifying genes involved in autosomal dominant polycystic kidney disease (ADPKD). Among these methods are those in involving mutagenizing nematodes that exhibit normal mating behavior; and identifying and selecting nematodes that exhibit altered mating behavior, where the altered mating behavior is manifested as an alteration in location of vulva and/or response to contact with the hermaphrodite. The mutated gene(s) responsible for the alteration in behavior are then identified. Databases or libraries of mammalian genes can be screened to identify homologs of these genes,

which can then serve as therapeutic or diagnostic targets or aid in elucidation of the disease pathology.

Methods for identifying compounds that are candidate therapeutic agents for treatment of autosomal dominant polycystic kidney disease

- 5 (ADPKD) are provided. Among the methods are those in which normal males are treated with a candidate compound. Compounds that result in changes in mating behaviors or changes in mating efficiencies are selected.

- 10 Methods for identifying genes involved in the disease pathway are also provided. Among the methods are those in which normal males are mutagenized. Offspring that exhibit changes in mating behaviors or changes in mating efficiencies are selected and mutated genes are identified and shown to be part of the pathway. Mammalian, particularly human, homologs of the mutated genes are then identified. Such genes
- 15 are likely to be part of the disease pathway. Such genes can serve as therapeutic targets and disease markers for diagnostic.

- Other assays use nematode strains that have mutations in either or both of *lov-1* or *pkd-2*. As described herein, suppressor and enhancer genetics can be used to assign functions to genes, to assign genes to
- 20 pathways, to identify the key switches in these pathways and to provide a sensitive assay to identify new genes in a pathway and lead compounds that modulate the activity of genes and/or gene products in the pathway.

- Assays that identify the role of PKD proteins in sensory function are also provided. Since *lov-1* and *pkd-2* are expressed in CEM neurons,
- 25 they have activity in other sensory functions, such as finding the mating partner at a distance. Accordingly assays using sexual chemotaxis or kinesis are provided. For example, males that are mutagenized or treated with a test compound are placed on a surface containing males and hermaphrodites, and are then observed to assess whether they can
- 30 choose between males and hermaphrodites. If the male is defective in

this sensory function, it will not distinguish between males and hermaphrodites.

- Assays that use dominant negative forms of PKD in nematodes or in other cells to identify mutations and/or compounds that inhibit PKD function are also provided. Transgenic nematodes that express a version of the LOV-1 or PKD-2 protein that inhibits the activity of LOV-1 and/or PKD-2 as assessed by manifestation of the altered LOV and/or response phenotypic behavior(s) are used in these assays. Transgenic nematodes can be produced by any method known to those of skill in the art, including, but are limited to, injection of the nucleic acid into the embryos or cells of the animal. Transgenic nematodes that contain a dominant negative *lov-1* or *pkd-2* transgene are contacted with a test compound, and compounds that interfere with a remaining activity of the *LOV-1* or *PKD-2* protein are selected. Alternatively, these transgenic nematodes are mutagenized and mutants that lose a remaining activity are selected and the gene or mutation responsible for the loss or that contributes to the loss is identified.

- Assays based on localization and trafficking of LOV-1 and/or PKD-2 within a cell or cells are also provided. These assays can identify regulators and factors necessary for synthesis and transport of *LOV-1* and/or *PKD-2* proteins and employ strains in which LOV-1 and PKD-2 are expressed linked to a detectable label, such as a fluorescent protein. These strains are used to assess the effects of compounds or mutagenesis on the trafficking patterns of *LOV-1* and *PKD-2* and cellular location(s) of the proteins in the animal. Identified mutations can be mapped and the genes identified. If mammalian, particularly human, homologs of these identified genes exist, such genes can serve as therapeutic or diagnostic targets and can aid in elucidation of the disease in mammals, particularly humans.

- Assays for identification of transcriptional regulators of expression of *lov-1* and/or *pkd-2* are also provided. These assays screen for loss or

alteration of expression of either gene and use transgenic nematodes with a reporter gene, such as a gene encoding a FP or lacZ or other detectable product, linked to the nucleic acid encoding *lov-1* or *pkd-2*. The animal is mutagenized or treated with a test compound and loss of expression or

- 5 reduction in expression of either gene is assessed. These assays identify regulators of and factors that affect *lov-1* and *pkd-2* expression.

Mammalian, particularly human homologs of these regulators and factors are identified. Such regulators and factors can be therapeutic or diagnostic targets, and/or can aid in developing an understanding of the

- 10 development and progression of PKD in mammals.

Kits for performing the assays, particularly, the drug screening assays, are also provided. The kits include transgenic or wild-type nematodes or both that express either wild-type or a mutant or a transgenic form of *lov-1* and/or *pkd-2*. The nematodes may be on plates,

- 15 in wells or in any form suitable for the assays. Kits containing nucleic acid encoding either of the two genes or probes based upon these sequences or reporter gene constructions containing all or portions of either or both genes are also provided. The nucleic acids may be in solution, in lyophilized or other concentrated form, or may be bound to a
- 20 suitable substrate. The kits can include additional reagents for performing the assays, such reagents include any for performing any of the steps of the methods. The kits include instructions for performing the assays.

DESCRIPTION OF FIGURES

- Figure 1 depicts male mating behavior of *C. elegans*. The
- 25 hermaphrodite is larger than the male and her vulva is depicted as a slit on the ventral, posterior third of her body. The male tail is placed flush on the hermaphrodite, ventral side down. His spicules are depicted by a line in the tail. The hook is anterior to the spicules, the post cloacal sensilla is posterior. Sequence 1 illustrates wild-type male Lov. Sequence 2
- 30 represents hook ablated aberrant Lov behavior (passing and slow search).

Sequence 3 portrays *lov-1(sy552)* mutant behavior (passing and eventually stopping).

Figure 2 depicts the molecular nature of *lov-1*. **a**, Genetic and physical maps of the *lov-1* region on chromosome 2. Genetic markers are shown. Boundaries of a *lov-1* deletion (*mnDf21*) and non-deletion (*eDf21*) are indicated. + designate rescue of *lov-1(sy552)* mutant males. Numbers in parentheses indicate the ratio of rescuing stable lines to total stable lines examined. **b**, *lov-1* gene structure. Exons are boxed. Genefinder predicts two ORFs, ZK945.10 (9 exons) and ZK945.9 (19 exons). RT-PCR reveals *lov-1* corresponds to the combination of ZK945.10 and ZK945.9. The arrow indicates the 1059 bp deletion in *lov-1 (sy582Δ)* **c**, *lov-1::GFP* (green fluorescent protein) expression constructs, patterns, and phenotypes in wild-type background. **d**, *lov-1* encodes a membrane associated protein with homology to the polycystin and voltage-activated channel families. A schematic representation of LOV-1 is shown to demonstrate domains of the protein. These include the amino terminus that is serine/threonine rich with multiple potential glycosylation sites, an ATP/GTP binding domain (indicated by the asterisks), followed by two polycystin blocks of homology. Block 1 is exclusively homologous to PKD1, while Block 2 shows homology with all polycystins and also the family of voltage activated CA^{2+} channels. Block 1 is a conserved domain of unknown function, that also occurs at the N-terminus of most 5-lipoxygenases. Identity (%) and number of identical amino acids (in parentheses) between LOV-1 and a particular polycystin is indicated. Although LOV-1 lacks the carboxy terminal coiled-coil domain of all known polycystins, a coiled-coil is predicted in the middle of LOV-1 using the most stringent criteria for the COILS program (data not shown). Y73F8A.B + A was identified in a Blast search of unpublished sequences available through the Sanger Center and is more similar to PKD2 (30% identity, 48% similarity, 13% gaps over 752 aa) than LOV-1 (25% identity, 44% similarity, 14% gaps over 367 aa).

Figure 3 shows the *lov-1* and *pkd-2* genomic structures, constructs, rescue date and expression patterns; the line above *lov-1* indicates the 1,059 bp deletion in *lov-1*(*sy582Δ*); numbers in parentheses indicate the ratio of rescuing stable lines to the number of stable lines

5 examined, DN is dominant negative.

Figure 4 shows that *lov-1::GFP1* and PKD-2::GFP2 are colocalized to cell bodies and dendrites and are specifically expressed in adult male sensory neurons; the spicules, hook structure and posteriormost fan region autofluoresce; Arrows indicate neuronal cell bodies and arrowheads

10 denote dendrites or ciliated endings. **a-c** *lov-1::GFP1*: (a) HOB and ray cell bodies (arrows), HOB dendritic process (arrowhead); (b) HOB and ray process 5 (arrowheads); (c) Ciliated endings in nose tip from male specific cephalic CEM neurons (cell bodies not shown). **d-f** *pkd-2::GFP2*: (d) ray cell bodies (arrow) and ray process 2 (arrowhead); (e) ray process

15 5 (arrowhead); (f) male-specific cephalic CEM ciliated endings (arrow)

Scale bar corresponds to 20 μ m.

DETAILED DESCRIPTION

Definitions

Unless defined otherwise, all technical and scientific terms used

20 herein have the same meaning as is commonly understood by one of skill in the art to which this invention belongs. *Caenorhabditis elegans* nomenclature is well understood by those of skill in this area (see, *e.g.*, *Methods in Cell Biology C. elegans* I, and II, Cold Spring Harbor Press Books, Shakes, Epstein eds).

25 All patents, patent applications and publications referred anywhere herein, including the background, are, unless noted otherwise, incorporated by reference in their entirety. In the event a definition in this

section is not consistent with definitions elsewhere, the definition set forth in this section will control.

As used herein, nematode is intended to refer generally to the class Nematoda or Nematoidea and includes those animals of a slender

- 5 cylindrical or thread-like form commonly called roundworms. Among those species, members of the genus *Caenorhabditis* are preferred, but species that can be cultured in the laboratory may be used.

- As used herein, the term "mutant," as in "nematode mutant" or "mutant nematode," is intended to refer generally to a nematode which
10 contains an altered genotype, preferably stably altered. The altered genotype results from a mutation not generally found in the genome of the wild-type nematode.

- As used herein, a mutant gene, such as a mutant *lov-1* or *pkd-2* gene, refers to a gene that is altered, whereby a nematode with such
15 gene, expresses an altered phenotype compared to a nematode with the wild type gene, such as a the genes set forth in SEQ ID Nos. 3 and 5 (which set forth the non-coding strands). Mutations include point mutations, insertions, deletions, rearrangements and any other change in the gene that results in an altered phenotype. Deletion mutants that
20 eliminate the function of the encoded protein (knock-out mutations) are exemplified herein. Not all mutations necessarily completely destroy the activity of the protein.

- As used herein, "normal mating behavior" means that the animal exhibits behavior typical of wild-type nematodes with respect to the
25 location of vulva (Lov) and response to of males to hermaphrodites. Thus a male that exhibits "normal mating behavior" upon encountering a hermaphrodite, ceases forward motion, places his tail flush on the hermaphrodite, commences backing along her body, and turns at her ends until he encounters her vulva and stops. This is the behavior of a *lov-*
30 *1(+)* male. Mutant males defective in *lov-1* frequently do not respond to contact with the hermaphrodite and continue blindly moving forward.

When response is initiated, *lov-1* mutants back and turn normally but pass the vulva at a high frequency. Thus, they can mate with paralyzed or otherwise slow moving hermaphrodites.

As used herein, a mammalian homolog of a nematode gene refers to a gene that encodes a protein that exhibits identifiable sequence homology and conservation of structure. The degree of sequence homology between a mammalian and nematode protein or gene to be considered homologs, depends upon the gene considered but is typically at least about 30% at the protein level. An ortholog will typically have greater sequence similarity, and conservation of structure and often function. Methods and criteria for identifying mammalian, including human, homologs of nematode genes are known to those of skill in the art and involve a comparison of the sequence and structural features of the encoded protein.

As used herein, a dominant negative mutation is a mutation that encodes a polypeptide that when expressed disrupts that activity of the protein encoded by the wild-type gene (see, Herskowitz (1987) *Nature* 329:219-222). The function of the wild-type gene is blocked, a cloned gene is altered so that it encodes a mutant product that inhibits the wild-type gene product in a cell or organism. As a result, the cell or organism is deficient in the product. The mutation is "dominant" because its phenotype is manifested in the presence of the wild-type gene, and it is "negative" in the sense that it inactivates the wild-type gene function. It is possible to do this because proteins have multiple functional sites.

As used herein, a "library" of nematodes is a collection of a plurality of nematodes, typically more than 10, preferably more than 100. Typically a library will include variety of different nematodes and may include wild-type and mutant nematodes and a sufficient number to achieve the intended purpose for which the library is used..

As used herein, a gene encoding *LOV-1* protein refers to a gene (a sequence of nucleotides including introns, and exons, and optionally

transcriptional regulatory sequences) from any nematode that encodes a protein that performs the same function in the nematode as the LOV-1 protein provided herein. Such protein can be identified using the methods provided herein for identifying it in *C. elegans*, or by isolating

- 5 cDNA encoding the protein using probes constructed from the nucleic acid provided herein to isolate it using standard methods. Typically the coding sequence of the gene provided herein will hybridize along its length to the coding sequence of a related gene under conditions of at least low stringency, preferably moderate stringency, and likely under
- 10 conditions of high stringency. Nucleic acid encoding a LOV-1 protein includes any nucleic acid molecule, DNA, cDNA, RNA, that encodes a protein that has substantially the sequence of amino acids set forth in SEQ ID No. 4 and encodes a protein that has the same activity as this protein. Minor sequence variations from species to species and even
- 15 among a species are considered to be substantially the same sequence. Such nucleic acid will hybridize to the nucleic acid encoding the proteins provided herein under conditions of at least low stringency, preferably moderate stringency and more preferably high stringency.

- 20 As used herein, a gene encoding *PKD-2* protein from a nematode is similarly defined, except that it has the substantially the same sequence as the sequence of amino acids set forth in SEQ ID No. 6. Having identified these proteins and functions therefor in *C. elegans* permits similar identification in other nematode species.

- 25 As used herein, stringency conditions refer to the washing conditions for removing the non-specific probes and conditions that are equivalent to either high, medium, or low stringency as described below:

- 1) high stringency: 0.1 x SSPE, 0.1% SDS, 65°C
- 2) medium stringency: 0.2 x SSPE, 0.1% SDS, 50°C
- 3) low stringency: 1.0 x SSPE, 0.1% SDS, 50°C.

- 30 It is understood that equivalent stringencies may be achieved using alternative buffers, salts and temperatures.

As used herein, percentage or amount or degree of sequence identity is used interchangeable with homology and refers to sequence identity or homology determined using standard alignment programs with gap penalties and other parameters set to the manufacturer's default settings. It is understood that for relatively high levels of sequence identity or homology, the particular program selected and/or defaults set for various parameters, do not substantially affect the results. Hence, for example, a requirement for 90% sequence identity of a nucleic acid sequence with another can be determined using any program known to the skilled artisan or manually, and that such percentage can encompass about 85% to 95% identity.

As used herein, reference to a drug refers to a chemical entity, whether in the solid, liquid, or gaseous phase that is capable of providing a desired therapeutic effect when administered to a subject. The term "drug" should be read to include synthetic compounds, natural products and macromolecular entities such as polypeptides, polynucleotides, or lipids and also small molecules, including, but are not limited to, neurotransmitters, ligands, hormones and elemental compounds. The term "drug" is meant to refer to that compound whether it is in a crude mixture or purified and isolated.

As used herein, heterologous or foreign DNA and RNA are used interchangeably and refer to DNA or RNA that does not occur naturally as part of the genome in which it is present or which is found in a location or locations in the genome that differ from that in which it occurs in nature. Heterologous nucleic acid is generally not endogenous to the cell into which it is introduced, but has been obtained from another cell or prepared synthetically. Generally, although not necessarily, such nucleic acid encodes RNA and proteins that are not normally produced by the cell in which it is expressed. Any DNA or RNA that one of skill in the art would recognize or consider as heterologous or foreign to the cell in which it is expressed is herein encompassed by heterologous DNA.

Examples of heterologous DNA include, but are not limited to, DNA that encodes exogenous invertase. Heterologous DNA and RNA may also encode RNA or proteins that mediate or alter expression of endogenous DNA by affecting transcription, translation, or other regulatable

5 biochemical processes.

As used herein, operative linkage of heterologous DNA to regulatory and effector sequences of nucleotides, such as promoters, enhancers, transcriptional and translational stop sites, and other signal sequences refers to the relationship between such DNA and such

10 sequences of nucleotides. For example, operative linkage of heterologous DNA to a promoter refers to the physical relationship between the DNA and the promoter such that the transcription of such DNA is initiated from the promoter by an RNA polymerase that specifically recognizes, binds to and transcribes the DNA in reading frame.

15 As used herein, a gene containing a heterologous transcriptional or translational or processing control region(s) refers to a nucleic acid molecule or construct that includes coding portion of a gene operatively linked to a such region derived from a different gene. A homologous transcriptional or translational or processing control region(s) refers to a

20 nucleic acid molecule or construct that includes coding portion of a gene operatively linked to a such region derived from the same gene.

As used herein, a promoter region refers to the portion of DNA of a gene that controls expression of DNA to which it is operatively linked.

The promoter region includes specific sequences of DNA that are

25 sufficient for RNA polymerase recognition, binding and transcription initiation. This portion of the promoter region is referred to as the promoter. In addition, the promoter region includes sequences that modulate this recognition, binding and transcription initiation activity of the RNA polymerase. These sequences may be cis acting or may be

30 responsive to trans acting factors. Promoters, depending upon the nature of the regulation, may be constitutive or regulated. A constitutive

promoter is always turned on. A regulatable promoter requires specific signals to be turned on or off. A developmentally regulated promoter is one that is turned on or off as a function of development.

As used herein, regulatory sequences include, sequences of

5 nucleotides that function, for example as transcriptional and translational control sequences. Transcriptional control sequences include the promoter and other regulatory regions, such as enhancer sequences, that modulate the activity of the promoter, or control sequences that modulate the activity or efficiency of the RNA polymerase that recognizes the

10 promoter, or control sequences are recognized by effector molecules, including those that are specifically induced by interaction of an extracellular signal with a cell surface protein. For example, modulation of the activity of the promoter may be effected by altering the RNA polymerase binding to the promoter region, or, alternatively, by interfering

15 with initiation of transcription or elongation of the mRNA. Such sequences are herein collectively referred to as transcriptional control elements or sequences. In addition, transcriptional controls sequences, include sequences of nucleotides that alter translation of the resulting mRNA, thereby altering the amount of a gene product.

20 As used herein, a reporter gene refers to a gene that encodes a detectable product. Such genes are well known to those of skill in the art and include, but are not limited to, genes encoding fluorescent proteins, particularly the well-known green fluorescent proteins, *lacZ*, enzymes and other such reporters known to be expressible and detectable in

25 nematodes. These genes are linked to a gene of interest whereby upon expression a detectable fusion protein is produced. For purposes herein, such fusions are exemplified using an aequorin GFP (see, Chalfie *et al.* (1994) *Science* 263:802-805; see, also U.S. Patent No. 5,741,668), but any such protein may be used. For example, GFP from *Aequorea victoria*

30 contains 238 amino acids, absorbs blue light and emits green light; it has

been cloned and its sequence characterized; various mutants are also well known. Nematode optimized codons may be selected.

As used herein, a reporter gene construct is a nucleic acid molecule that includes a reporter gene operatively linked to transcriptional control
 5 sequences. Typically the construct will also include all or a portion of a the gene of interest, which herein is *lov-1* and/or *pkd-2*, and the reporter gene will be under the control of the *lov-1* or *pkd-2* promoter and other regulatory regions. By operatively linked is meant linked whereby an in-frame fusion protein is produced upon expression of the construct and
 10 whereby the reporter gene product is active (*i.e.* produces a detectable signal or is active). The reporter gene may be linked to the 3' or 5' end or in any other orientation whereby it is expressed and operates as a reporter.

As used herein, isolated, substantially pure DNA refers to DNA
 15 molecules or fragments purified according to standard techniques employed by those skilled in the art, such as those described in Sambrook *et al.* (1989) *Molecular Cloning: A Laboratory Manual*, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY).

As used herein, expression refers to the process by which nucleic
 20 acid is transcribed into mRNA and translated into peptides, polypeptides, or proteins. If the nucleic acid is derived from genomic DNA, expression may, if an appropriate eukaryotic host cell or organism is selected, include splicing of the mRNA.

As used herein, cloning vehicle or vector, which are used
 25 interchangeably, refers to a plasmid or phage DNA or other DNA molecules that replicate autonomously in a host cell, and that include one or a small number of endonuclease recognition sites at which such DNA may be cut in a determinable fashion without loss of an essential biological function of the vehicle, and into which DNA may be spliced in
 30 order to bring about its replication and cloning. The cloning vehicle may further contain a marker suitable for use in the identification of cells

transformed with the cloning vehicle. Markers, include but are not limited to, tetracycline resistance and ampicillin resistance.

Appropriate expression vectors are well known to those of skill in the art and include those that are replicable in eukaryotic cells and/or

5 prokaryotic cells. Such expression vectors may remain episomal or may integrate into the host cell genome. Expression vectors suitable for introducing heterologous DNA into plants and into host cells in culture, such as mammalian cells and methylotrophic yeast host cells, are known to those of skill in the art. It should be noted that, because the functions
10 of plasmids, vectors and expression vectors overlap, those of skill in the art use these terms, plasmid, vector, and expression vector, interchangeably. Those of skill in the art, however, recognize what is intended from the purpose for which the vector, plasmid or expression vector is used.

15 As used herein, integrated into the genome means integrated into a chromosome or chromosomes.

As used herein, a "fragment" of a protein refers to any portion of a protein that contains less than the complete amino acid sequence of the protein but that retains a biological or chemical function of interest.

20 As used herein, expression vector or expression vehicle refers to such vehicle or vector that capable, after transformation into a host, of expressing a gene cloned therein. The cloned gene is usually placed under the control of (i.e., operably linked to) certain control sequences such as promoter sequences. Expression control sequences will vary
25 depending on whether the vector is designed to express the operably linked gene in a procaryotic or eukaryotic host and may additionally contain transcriptional elements such as enhancer elements, termination sequences, tissue-specificity elements, and/or translational initiation and termination sites.

30 As used herein, a variant of a protein refers to a protein substantially similar in structure and biological activity to

either the entire protein or a fragment thereof. Thus, provided that two proteins possess a similar activity, they are considered variants as that term is used herein even if the composition or secondary, tertiary, or quaternary structure of one of the molecules is not identical

- 5 to that found in the other, or if the sequence of amino acid residues is not identical.

It is also understood that any of the proteins or portions disclosed herein may be modified by making conservative amino acid substitutions and the resulting modified subunits are contemplated herein. Suitable
 10 conservative substitutions of amino acids are known to those of skill in this art and may be made generally without altering the biological activity of the resulting molecule. Those of skill in this art recognize that, in general, single amino acid substitutions in non-essential regions of a polypeptide do not substantially alter biological activity (see, e.g., Watson
 15 et al. *Molecular Biology of the Gene*, 4th Edition, 1987, The Benjamin/Cummings Pub. Co., p.224). Such substitutions are preferably, although not exclusively, made in accordance with those set forth in TABLE 1 as follows:

20

TABLE 1

Original residue	Conservative substitution
Ala (A)	Gly; Ser
Arg (R)	Lys
Asn (N)	Gln; His
25 Cys (C)	Ser
Gln (Q)	Asn
Glu (E)	Asp
Gly (G)	Ala; Pro
His (H)	Asn; Gln
30 Ile (I)	Leu; Val
Leu (L)	Ile; Val
Lys (K)	Arg; Gln; Glu
Met (M)	Leu; Tyr; Ile
Phe (F)	Met; Leu; Tyr
35 Ser (S)	Thr
Thr (T)	Ser
Trp (W)	Tyr
Tyr (Y)	Trp; Phe
40 Val (V)	Ile; Leu

40 Comparable mutations may be made at the nucleotide sequence level.

Other substitutions are also permissible and may be determined empirically or in accord with known conservative substitutions. Any such modification of the polypeptide may be effected by any means known to those of skill in this art. Mutation may be effected by any
5 method known to those of skill in the art, such as by chemicals or radiation, and also including site-specific or site-directed mutagenesis of DNA encoding the protein and the use of DNA amplification methods using primers to introduce and amplify alterations in the DNA template.

As understood by those skilled in the art, assay methods for
10 identifying compounds, such as antagonists and agonists, that modulate functioning of a protein or protein or pathway, generally require comparison to a control. One type of a "control" system is one that is treated substantially the same as the system, such as a worm, exposed to the test compound except that the control is not exposed to the test
15 compound. Another type of a control may be one that is identical to the test system, except that it does not express the gene or protein of interest. In this situation, the response of a test system is compared to the response (or lack of response) of the control to the test compound, when each cell is exposed to substantially the same reaction conditions in
20 the presence of the compound being assayed.

As used herein, treatment means any manner in which the symptoms of a condition, disorder or disease are ameliorated or otherwise beneficially altered.

As used herein, amelioration of the symptoms of a particular
25 disorder by administration of a particular pharmaceutical composition refers to any lessening, whether permanent or temporary, lasting or transient that can be attributed to or associated with administration of the composition.

As used herein, a composition refers to any mixture of two or more
30 components. It may be solution, suspension, or any other mixture.

As used herein, biological activity refers to the in vivo activities of a compound or physiological responses that result upon in vivo administration of a compound, composition or other mixture. Biological activity, thus, encompasses therapeutic effects and pharmaceutical activity of such compounds, compositions and mixtures.

Nematodes as disease models

Nematodes serve as model organisms for the study of gene expression. *Caenorhabditis elegans* is representative of nematodes. It is a small, freeliving bacteriovorous soil nematode that is a member of the *Rhabditidae*, a large and diverse group of nematodes found in terrestrial habitats. Some rhabditids are pathogenic to or parasitic on animals. In common with other nematodes, *C. elegans* develops through four larval stages (also called juveniles) that are separated by moults. The lifecycle takes about 3 days at 20 ° C.

C. elegans is only 1 mm long and can be handled in a manner similar to microorganisms, including growth on petri plates seeded with bacteria. In the laboratory, *C. elegans* is fed on *E. coli*. It has a transparent body and all somatic cells (959 female; 1031 male) are visible with a microscope.

Although it is a primitive organism, it shares many of the essential biological characteristics, including embryogenesis, morphogenesis, development and aging that are central problems of human biology. The worm is conceived as a single cell that undergoes a complex process of development, starting with embryonic cleavage, proceeding through morphogenesis and growth to the adult. It has a nervous system with a 'brain' (the circumpharyngeal nerve ring), It exhibits definable behaviors, and is capable of rudimentary learning. It produces sperm and eggs, mates and reproduces. After reproduction it gradually ages, loses vigor and dies. Its average life span is 2-3 weeks.

Adult *C. elegans* are usually self-fertilizing protandrous hermaphrodites. As a result homozygous mutant stocks can be readily

generated. The hermaphrodite gonad first produces germ cells that differentiate as sperm (about 250 sperm are produced) and then produces eggs. The fecundity is determined by the sperm supply.

- Nematodes, particularly *C. elegans*, is one of the most thoroughly
- 5 understood of all multicellular organisms. The biology of its nervous system, which contains 302 neurons, is well-documented. Many *C. elegans* genes used have counterparts in mammals, including humans. At least half of the *C. elegans* genes and proteins that have been characterized have structures and functions similar to mammalian genes.
- 10 These include genes encode enzymes, proteins necessary for cell structure, cell surface receptors and genetic regulatory molecules.

- Animals from man to worm have most of their protein families in common and humans frequently have four to five close analogs of a protein family member, where worms have only one. Essentially all
- 15 genes and pathways shown to be important in cell-, developmental- and disease-biology have been found to be conserved between worm and human. This conservation applies to the number and type of protein families, gene structure, the hierarchy of genes in genetic pathways and even gene regulation.

- 20 A consequence of this conservation is that human genes can be inserted into the worm genome, to functionally replace the worm genes even in complex cell biological and signal transduction pathways. Conversely, key worm genes identified using genetics can be used to trigger specific biochemical processes in human cells and to serve as
- 25 models for the human genes.

Genetics Nomenclature

- C. elegans* is diploid and has five pairs of autosomal chromosomes (designated I, II, III, IV and V) and a pair of sex chromosomes (X) that determine gender. XX is a hermaphrodite and XO is male. Males are
- 30 found rarely (about 0.05% of normal lab populations). The commonest lab strain, and the designated "wild-type" strain, is called N2.

For historical reasons *C. elegans* nomenclature is different from other species. Loci have a 3-letter dash one number designation. The letters are an acronym for the phenotype and the number is consecutive. Alleles have a single or double letter followed by a number. The letter identifies the isolating laboratory. Strains have a letter(s) number designation. The letters identify the isolating laboratory (*i.e.* AB100 abc-1(xy1000) Strain AB100 which carries the xy1000 allele of abc-1. The chromosomal location can be added: AB100 abc-1(xy1000) I. Multiple mutant alleles carried in one strain are organized by chromosome, and chromosomes separated by semicolons. Heterozygous nematodes are designated by a abc-1/+ notation. Hence abc-1(+) indicates the wild-type (N2 strain) copy of the gene. Proteins are capitalised and not italicized. ABC is the protein product of abc-1.

Rearrangements, duplications and deficiencies have a letter prefix (indicating the isolating lab) a Dp (pronounced dupe, for duplication) or Df (pronounced dif for deficiency) and a number (*i.e.*, xyDp1 is duplication number 1 from xy and xyDf1 is deficiency number 1 from xy lab). Transgenic strains carrying the transgene as a free extrachromosomal array are designated as follows: xyEx1[abc-1(+)] is a transgenic strain carrying the wt copy of abc-1.

The *C. elegans* Genome

The *C. elegans* genome, which is 97 Mb, contains six approximately equally sized chromosomes (5 autosomes, one X) and it has been sequenced (see, (1998) *Science* 282:2012-2018) and is publicly available. The 97 Mb encodes a predicted 19,099 protein-encoding genes; although as shown herein, there remain ambiguities. Over 60,000 cDNA fragments have been tag sequenced and 101000 ESTs deposited. These "expressed sequence tags" or ESTs offer a set of snapshots of gene expression in the nematode, and have identified around half of the organism's genes. The cDNA data is used in the prediction of genes from the genome sequence along with database

- searches for similarities between *C. elegans* genes and those of other organisms such as humans. This estimate is based on the correspondence between genomic DNA sequence and cDNA sequences, and on the prediction of coding genes from genomic sequence. The genome data (and
- 5 much else besides) is collated into an available database ACeDB, written for the *C. elegans* project. A physical map of the genome, which is publically available in the *C. elegans* genome database ACeDB, has been constructed. The map is based on 17,000 cosmid clones of genomic DNA (insert size 35-40 kb). These clones were "fingerprinted" using
- 10 restriction enzymes, and the fingerprints used to order the clones in overlapping contiguous sets, or contigs. These cosmid contigs have been supplemented by a set of 3,000 yeast artificial chromosome clones (insert sizes 100 kb and above). Because the yeast host tolerates sequences that *E. coli* does not, the YAC clones can "bridge" gaps between contigs of
- 15 cosmids. With these two resources, contigs covering >95% of all the chromosomes have been assembled. The clones are freely available for researchers, and the 3,000 YAC clones are available as an array on a filtermat, arranged in approximate chromosomal order, for screening purposes.
- 20 The genomes of other nematodes are in the same size range. *Brugia malayi*, a filarial parasite of humans, has a genome of 100 Mb; *Ascaris suum*, the pig roundworm, has a larger germ line genome which undergoes somatic diminution.

25 **Identification of the genes associated with the location of vulva and response behaviors**

The behaviors

- The six sub-steps of the stereotyped copulatory sequence has been correlated with the function of individual neurons, and behavioral mutants have been isolated (Liu *et al. Neuron* 14:79-89). *C. elegans* male mating
- 30 behavior includes a series of steps: response to contact with the hermaphrodite, backing along the body of the hermaphrodite, turning

around her head or tail, location of the vulva, insertion of the two copulatory spicules into the vulva and sperm transfer. Sensory structures and neurons that participate in each of these steps have been identified: the sensory rays mediate response to contact and turning; the hook, the postcloacal sensilla and the spicules mediate vulva location; and the spicules also mediate spicule insertion and regulate sperm transfer.

Thus, the stereotyped mating behavior of the *Caenorhabditis elegans* male comprises several substeps: response backing, turning, vulva location, spicule insertion, and sperm transfer (Fig. 1). The complexity of male mating behavior is reflected in the sexually dimorphic anatomy and nervous systems of the male and hermaphrodite (Hodgkin, J. (1988) in *The Nematode C. elegans* (ed. Wood, B.) pp. 243-279 (Cold Spring Harbor Laboratory Press, New York). Behavioral functions have been assigned to most male-specific sensory neurons via cell ablations (Liu *et al. Neuron* 14:79-89). Although the hermaphrodite is behaviorally passive, her vulva provides sensory cues to the male.

Vulva location behavior is complex. The male stops and precisely positions his tail over the vulva, coordinates his movement to the hermaphrodite's, and ultimately insert his spicules into the vulva slit and transfers sperm into the uterus. The hook sensory neurons, HOA and HOB, are specifically required for location of vulva (Lov) behavior. Ablation of either HOA or HOB results in a Lov defect whereby the ablated male circles the hermaphrodite without stopping at the vulva (Fig. 1). Eventually, the ablated male begins an alternative search by backing slowly and prodding randomly with his spicules until the vulva is located. The postcloacal sensilla are required for slow search behavior. Vulva location behavior is executed by a minimum of eight sensory neurons with overlapping and redundant functions (Liu *et al. Neuron* 14:79-89).

A genetic analysis of vulva location behavior to investigate how genes specify sensory behavior, beginning with sensory reception was

performed. The mating behavior of existing mutants defective in sensory behaviors including chemotaxis to soluble and volatile odorants, mechanosensation, and osmotic avoidance was first examined. From this survey, it was found that only males with severe defects in all sensory

5 neuron cilia (*osm-4*, *osm-5*, *osm-6*, and *che-3*) were Lov defective (Table 2). For example, *osm-6(p811)* males locate the vulva with an efficiency of 32% versus 96% of wild-type (Table 2). These males are also response defective, but not so severely as to prevent observation of the Lov phenotype. The only ciliated cells in *C. elegans* are

10 chemosensory and mechanosensory neurons (White *et al.* (1986) *Philos. Trans. R. Soc. Lond. B Biol. Sci.* 314:1-340). The male tail possesses thirty predicted ciliated sensory neurons (Sulston *et al.* (1980) *Dev. Biol.* 78:542-576), consistent with the observation that ciliated neurons modulate response and Lov. *osm-6::gfp* is expressed exclusively in

15 ciliated neurons, with male-specific expression in four CEM head neurons and neurons of the rays and copulatory spicules (Collet *et al.* (1998) *Genetics* 148:187-200). More detailed examination revealed that *osm-6::gfp* expression begins at the L4 stage in neuronal cell bodies and extends to dendrites as neuronal outgrowth proceeds (data not shown).

20 The RnA and RnB neurons of each ray (ray 1 through ray 9), the HOA and HOB hook neurons, the spicule neurons SPV and SPD, and the PCB postcloacal sensilla neurons accumulate GFP. The *osm-6* expression pattern and mutant phenotypes indicate that OSM-6 might be required for the structure and function of ciliated neurons in the adult male tail. In the

25 hermaphrodite, *osm-6* function is required for nose touch (Kaplan *et al.* (1993) *Proc. Natl. Acad. Sci. U.S.A.* 90:2227-2231), osmotic avoidance, chemotaxis, dye-filling of sensory neurons, thermotaxis, dauer formation, and proper assembly of ciliated sensory endings (Perkins *et al.* (1986) *Dev. Biol.* 117:456-487). Hence, ciliated endings are important for all

30 known sensory behaviors, including Lov.

TABLE 2. Vulva location behavior of wild-type and mutant males

	Genotype	vulva location efficiency %	Significantly different from wild-type (p value)		[†] n
5	<i>him-5</i> (wild-type)	96	—	—	101
	<i>osm-1(e1803)</i>	65	No	(0.0738)	
	<i>osm-4(p821)</i>	48	Yes	(0.0004)	
	<i>osm-5(p813); him-5</i>	26	Yes	(0.0002)	
	<i>osm-6(p811)</i>	32	Yes	(0.0003)	
10	<i>che-3(e1124)</i>	69	Yes	(0.02666)	
	<i>lov-1(sy582Δ)</i>	11	Yes	(<0.0001)	
	<i>lov-1(sy582); him-5</i>	30	Yes	(<0.0001)	

Table 2. *lov-1(sy522); him-5(e1490)*, *lov-1(sy582Δ)*, and all cilia defective mutant were also response defective. Males that eventually responded were scored for Lov behavior.

[†]n represents the number of males observed, each for a minimum of 10 vulva encounters per male. Mann-Whitney tests determined p values. The following non-cilia-defective osmotic avoidance (*osm*), mechanosensory defective (*mec*), chemosensory defective (*che*), odorant response abnormal (*odr*) and dauer formation defective (*daf*) mutants were also examined and found to be normal for response and Lov behavior: *osm-3(e1806); him-5(e1490)*, *osm-7(n1515)*, *osm-8(n1518)*, *osm-10(n1604)*, *osm-11(n1604)*, *osm-12(n1606)*, *mec-3(e1338)*, *him-8(e1489)*, *mec-4(e1611)*, *mec-5(e1340)*, *mec-7(n434)*, *mec-7(e1343)*, *mec-8(e398)*, *mec-9(e1494)*, *che-112*, *odr-1(n1936)*, *odr-2(n2145)*, *odr-3(n2150)*, *odr-4(n2144ts)*, *odr-5*, *odr-6(kyl)*, *odr-7(ky4)*, *odr-10(ky32)* and *daf-11(m47ts)*.

Provided herein are mutants that are defective in location of the vulva (Lov). Lov mutant males are unable to execute this step. In addition, these males are also defective in the first sub-step, 'response'. Response and vulva location depend on two types of male sensory structure: the first is a set of nine pairs of rays, which project out of the tail on each side; and the second is a hardened cuticular structure called the hook, which contains two sensory neurons. These mutants were used to identify the genes involved in these behaviors.

Identification and cloning of the *lov-1* gene

To elucidate the molecular basis of behavior and sensory the mutants are studied and genes associated with the behaviors are identified. A gene designated *lov-1* that is required for two male sensory behaviors, response and location of vulva (Lov) is described herein. It is also associated with other sensory behaviors controlled by the CEM neurons.

This gene, *lov-1*, encodes a putative membrane protein with a mucin-like, serine-threonine rich amino terminus (Carraway *et al.* (1995) *Trends Glycoscience Glycotechnology* 7:31-44) followed by two blocks of homology to human polycystins encoded by the autosomal dominant polycystic kidney disease (ADPKD) genes (Torres *et al.* (1998) *Current Opinion in Nephrology and Hypertension* 7:159-169). LOV-1 and human PKD1 are 26% identical in block 1. Block 2 also shows 20% identity between LOV-1, all identified polycystins (PKD1, PKD2, and PKDL), and the family of voltage-activated channels (Torres *et al.* (1998) *Current Opinion in Nephrology and Hypertension* 7:159-169). Overall, LOV-1 is the closest *C. elegans* homolog of PKD1. The polycystin/channel domain (block 2) of LOV-1 is required for function. *Lov-1* is specially expressed in adult male sensory neurons of the rays, hook, and head, mediating response, Lov, and potentially chemotaxis to hermaphrodites, respectively (Liu *et al.* *Neuron* 14:79-89, Ward *et al.* (1975) *J. Comp. Neurol.* 160:313-337). Localization of *lov-1* to neuronal cell bodies and ciliated sensory endings is consistent with a role in either chemo- and/or mechanosensory reception and signaling. Human PKD proteins might similarly be involved in sensory reception during osmoregulation, organogenesis and/or organ maintenance.

Cloned genes and encoded proteins

To identify genes specifically required for male sensory behaviors, mutants defective in Lov were screened. *Lov-1(sy552)* males have specific response and Lov defects. Upon encountering a hermaphrodite, a *lov-1(+)* male ceases forward motion, places his tail flush on the hermaphrodite, commences backing along her body, and turns at her ends until he encounters her vulva and stops. Mutant males defective in *lov-1* frequently do not respond to contact with the hermaphrodite and continue blindly moving forward. When response is initiated, *lov-1* mutants back and turn normally but pass the vulva at a high frequency. The response and vulva location ability of *lov-1(sy552)* is 30% that of *lov-1(+)* males

(Table 2). Spicule insertion and sperm transfer behaviors are unaffected. *lov-1(sy552)* males exhibit high mating efficiency with severely paralyzed *unc-52* hermaphrodites but sire few progeny with actively moving *dpy-17* hermaphrodites. Differences between mating efficiencies is partner-dependent. A paralyzed partner is an easier target for the *lov-1* mutant male who is defective in response and Lov but unimpaired in the behaviors of backing, turning, spicule insertion, and sperm transfer. The behavioral defects of *sy552* are limited to male mating. *Lov-1(sy552)* mutants appear normal for other sensory behaviors including egg laying, nose touch, tap, mechanosensation, and osmotic avoidance.

The *lov-1* gene was cloned by genetic mapping and transformation rescue of the *sy552* behavioral defects (Fig. 2a). *mnDf2/sy552*, *mnDf83/sy552* and *sy552/sy552* males are phenotypically indistinguishable; therefore, *sy552* is reduction or loss of function mutation in *lov-1*. This conclusion is supported by the observed recessive nature of *sy552*. A 16.9 kb HindIII subclone (plov-1.1) of the cosmid ZK945 rescued response and Lov defects of *sy552* (Fig. 2a). Both a 6.7 kb HindIII-BamHI fragment from plov-1.1 (plov-1::GFP1) and a 14.1 kb HindIII-StuI frameshift in plov-1.1 (plov-1.3) fail to rescue *sy552* defects (Fig. 2b) yet act in a dominant negative (DN) manner in wild-type males with respect to Lov behavior (Fig. 2c). Wild-type males expressing either plov-1::GFP or plov-1.3 are Lov defective. These transgenic males exhibit a wild-type response to hermaphrodite contact. Without being bound by a theory, the differences in *sy552* and transgenic DN phenotypes might be attributed to dosage or mosaicism.

Figure 2b illustrates the intron-exon boundaries of the *lov-1* gene. Using RT-PCR with *lov-1* specific primers and *him-5* mRNA, it was found that *lov-1* encodes one transcript corresponding to Genefinder-predicted ORFs, ZK945.10 and ZK945.9 (Fig. 2b), which had been thought to be two genes. *Lov-1* encodes a predicted 3178 amino acid membrane-bound protein (see SEQ ID Nos. 3 and 4) with a serine-threonine rich

extracellular domain homologous to mucins (Carraway *et al.* (1995) *Trends Glycoscience Glycotechnology* 7:31-44), a polycystin homology block 1 (26% identity), and a carboxy terminal polycystin block 2 with 20% identity to polycystin proteins 1, 2, and 2, encoded by the PKD1, 5 PKD2, and PKDL (polycystic kidney disease) genes, respectively (Fig. 2d). A Kyte-Doolittle hydropathy plot predicts multiple transmembrane domains; although no signal peptide is predicted in LOV-1. Mucins are highly glycosylated extracellular proteins thought to serve cell adhesion and/or protective functions (Carraway *et al.* (1995) *Trends Glycoscience* 10 *Glycotechnology* 7:31-44).

Similarity between exons W (for PKD1 only), X, Y, Z, AA, BB, and CC of *lov-1* and PKD1, PKD2, and the family of voltage-activated calcium and potassium channels in the six transmembrane spanning region has been observed (Mochizuki *et al.* (1996) *Science* 272:1339-1342). This 15 extends to PKDL (Nomura *et al.* (1998) *J. Biol. Chem.* 273:25967-25973). LOV-1 lacks the Ca²⁺ binding EF-hand of polycystin 2 and L, and a coiled-coil domain of all three polycystins (Fig. 2d), which has been shown to mediate hetero- and homotypic interactions between polycystin 1 and polycystin 2 (Qian (1997) *Nature Genetics* 16:179-183; 20 Tsiokas *et al.* (1997) *Proc. Natl. Acad. Sci. USA* 94:6965-6970). Block 2 also shows limited homology with the trp (transient receptor potential) family of channels (Montell *et al.* (1989) *Neuron* 2:1313-1323). The critical difference between voltage-gated and trp channels is the presence of a positively charged S4 transmembrane domain that acts as a voltage 25 sensor (Montell *et al.* (1989) *Neuron* 2:1313-1323). LOV-1 more closely resembles voltage-gated channels in this respect. A frameshift disruption in *lov-1* (plov-1.3) one residue away from a corresponding nonsense mutation in human PKD2 (Mochizuki *et al.* (1996) *Science* 272:1339-1342) destroys the ability to rescue *lov-1*(sy552), as mentioned above. 30 The construct plov-1.3 encodes a truncated protein lacking the polycystin block 2/channel domain. These results demonstrate that the polycystin

block 2/channel domain is essential for LOV-1 function, and indicate that functional as well as structural similarities might exist between LOV-1 and PKD-2. LOV-1 also possesses a nucleotide-binding domain (Fig. 2d) that is not present in the human polycystins. The structure of LOV-1 is also
 5 indicative of a role in signal transduction.

The *lov-1* gene product appears to be a membrane spanning protein that includes an extracellular domain with a serine/threonine-rich mucin-like domain, an ATP-binding domain, and small cytoplasmic tails that mediate interaction with other members of the pathway, including a *pkd-2*
 10 gene product that is also a membrane spanning protein, with six membrane domains, and a cytoplasmic EF-hand. Interaction of these proteins lead to the observed phenotypic response. In *C. elegans* this response can be detected as a clearly identifiable phenotype. Hence, *C. elegans* and mutants thereof can serve as a test system for identifying
 15 compounds that alter this pathway and also for identifying other gene products involved in the pathway.

***lov-1* gene**

In an exemplary embodiment, the complement of the nucleic acid sequence of the *lov-1* gene from *C. elegans* is provided. Corresponding
 20 genes from other nematodes may be identified, such as by using the nucleic acid provided herein and screening an appropriate library, genomic or cDNA library, using standard procedures. Alternatively, databases of sequence may be searched and the genes from other nematodes homologous to those provided herein identified, again using standard
 25 searching and alignment programs.

SEQ ID NO. 3 is the complement of the genomic sequence of the *lov-1* gene. It includes open reading frames (ORFs) between nucleotides 15760 to 27880 of cosmid ZK945 (nucleotides 1 to 12121 of SEQ ID NO.3) and nucleotides 1-564 of cosmid F27E5 (nucleotides 12122 to
 30 12685 of SEQ ID NO.3). It was found herein, however, that ZK945 and F27E5 overlap from nucleotides 27881 to 27981 and nucleotides 1 to

101, respectively (the overlap region includes nucleotides 12122 to 12222 in SEQ ID NO.3), thereby providing a single, rather than two, ORFs.

It been thought that the open reading frame in cosmid ZK945 (the "ZK945.9" gene; nucleotides 1 to 9164 of SEQ ID NO.3), and the open reading from in cosmid F27E5 (the "ZK945.10" gene; nucleotides 9415 to 12685 of SEQ ID NO.3) encoded two genes. DNA sequence analysis of RT-PCR generated cDNA clones from *him-5(e1490)* RNA revealed three exons (**exons I, J and K** in Figure 2B) in the junction between ZK945.10 and ZK945.9: one from nucleotides 25195 to 25742 of the ZK945 cosmid (nucleotides 9436 to 9983 of SEQ ID NO. 3); a second from nucleotides 25071 to 25151 of the ZK945 cosmid (nucleotides 9312 to 9392 of SEQ ID NO. 3); and a third initiating at position 25021 in the ZK945 cosmid (nucleotide 9262 of SEQ ID NO. 3). This demonstrated that the *lov-1* gene encodes one large transcript corresponding to ORFs in ZK945.10 and ZK945.9, spanning what had previously been thought to encode two proteins.

As noted above, Figure 2B depicts the *lov-1* genomic structure (exons shown as boxes, introns as lines). With reference to Figure 2B, the coding sequence in the gene set forth in SEQ ID No. 3 (noting that SEQ ID 3 sets forth the non-coding strand) is as follows:

Complement (Join (12500...12685) - Exon A; (12266...12451) - Exon B; (12085...12217) - Exon C; (11683...11823) - Exon D; (11498...11637) - Exon E; (11128...11452) - Exon F; (10268...10899) - Exon G; (10138...10216) - Exon H; (9436...9983) - **Exon I**; (9312...9392) - **Exon J**; (8685...9262) - **Exon K**; (8557...8635) - Exon L; (7830...7997) - Exon M; (6774...7786) - Exon N; (6648...6728) - Exon O; (6305...6598) - Exon P; (6006...6255) - Exon Q; (5732...5958) - Exon R; (4849...5076) - Exon S; (4698...4799) - Exon T; (4383...4651) - Exon U; (3336...4328) - Exon V; (2229...3094) - Exon W; (1976...2181) -

101, respectively (the overlap region includes nucleotides 12122 to 12222 in SEQ ID NO.3), thereby providing a single, rather than two, ORFs.

It been thought that the open reading frame in cosmid ZK945 (the "ZK945.9" gene; nucleotides 1 to 9164 of SEQ ID NO.3), and the open reading from in cosmid F27E5 (the "ZK945.10" gene; nucleotides 9415 to 12685 of SEQ ID NO.3) encoded two genes. DNA sequence analysis of RT-PCR generated cDNA clones from *him-5(e1490)* RNA revealed three exons (**exons I, J and K** in Figure 2B) in the junction between ZK945.10 and ZK945.9: one from nucleotides 25195 to 25742 of the ZK945 cosmid (nucleotides 9436 to 9983 of SEQ ID NO. 3); a second from nucleotides 25071 to 25151 of the ZK945 cosmid (nucleotides 9312 to 9392 of SEQ ID NO. 3); and a third initiating at position 25021 in the ZK945 cosmid (nucleotide 9262 of SEQ ID NO. 3). This demonstrated that the *lov-1* gene encodes one large transcript corresponding to ORFs in ZK945.10 and ZK945.9, spanning what had previously been thought to encode two proteins.

As noted above, Figure 2B depicts the *lov-1* genomic structure (exons shown as boxes, introns as lines). With reference to Figure 2B, the coding sequence in the gene set forth in SEQ ID No. 3 (noting that SEQ ID 3 sets forth the non-coding strand) is as follows:

Complement (Join (12500...12685) - Exon A; (12266...12451) - Exon B; (12085...12217) - Exon C; (11683...11823) - Exon D; (11498...11637) - Exon E; (11128...11452) - Exon F; (10268...10899) - Exon G; (10138...10216) - Exon H; (9436...9983) - **Exon I**; (9312...9392) - **Exon J**; (8685...9262) - **Exon K**; (8557...8635) - Exon L; (7830...7997) - Exon M; (6774...7786) - Exon N; (6648...6728) - Exon O; (6305...6598) - Exon P; (6006...6255) - Exon Q; (5732...5958) - Exon R; (4849...5076) - Exon S; (4698...4799) - Exon T; (4383...4651) - Exon U; (3336...4328) - Exon V; (2229...3094) - Exon W; (1976...2181) -

Exon X; (1635...1930) - Exon Y; (1043...1591) - Exon Z; (625...999) - Exon AA; (329...572) - Exon BB; (1...270) - Exon CC).

The LOV-1 amino acid sequence is set forth in SEQ ID NO. 4. The following table summarizes the above.

5 TABLE 3 Comparison of Sequence ID No. 3 with source Cosmids[†]

EXON	SEQ ID 3	ZK945	F27E5
A	12500..12685		379..564
B	12266..12451		145..330
C	12085..12217	27844..27976	
D	11683..11823	27442..27582	
E	11498..11637	27257..27396	
F	11128..11452	26887..27211	
G	10268..10899	26027..26658	
H	10138..10216	25897..25975	
*I	9436..9983	25195..25742	
*J	9312..9392	25151..25071	
*K	8685..9262	24444..25021	
L	8557..8635	24316..24394	
M	7830..7997	23589..23756	
N	6774..7786	22533..23545	
O	6648..6728	22407..22487	
P	6305..6598	22064..22357	
Q	6006..6255	21765..22014	
R	5732..5958	21491..21717	
S	4849..5076	20608..20835	
T	4698..4799	20457..20558	
U	4383..4651	20142..20410	
V	3336..4328	19095..20087	
**W	2229..3094	17988..18853	
X	1976..2181	17735..17940	
Y	1635..1930	17394..17689	
Z	1043..1591	16802..17350	

EXON	SEQ ID 3	ZK945	F27E5
AA	625..999	16384..16758	
BB	329..572	16088..16331	
CC	1..270	15760..16029	

- 5 *exons I, J, K at the junction of ZK945.10 and ZK945.9 (as determined by RT-PCR analysis, and not predicted by the GeneFinder program)

**the *sy582 lov-1* mutant has a 1059 bp deletion beginning in exon W at position 2267 of SEQ ID NO. 3 (18026 of the ZK945 cosmid) and ending at position 1209 of SEQ ID NO. 3 (16968 of the ZK945 cosmid).

10

¹ The GenBank accession numbers for ZK945 and F27E5 are (GenBank Accession No. Z48544) and (GenBank Accession No. Z48582), respectively.

Exemplary knockout mutant *sy582*

- A genomic deletion of *lov-1* in a PCR screen of EMS mutagenized worms was isolated. *lov-1(sy582Δ)* encodes a truncated protein lacking the polycystin/cation channel homology domain (Fig. 2d). Like *sy552*, *lov-1(sy582Δ)* males exhibit defects in response and Lov behaviors (Table 2), as well as low mating efficiency with *dpy-17* but not *unc-52* partners. *sy582Δ* is recessive and fails to complement *sy552*. The truncated protein produced by *lov-1(sy582Δ)* does not act as a dominant negative in contrast to the truncated protein produced by *plov-1.3* (see below). This difference might be due to a dosage effect of the *plov-1.3* transgene. These results confirm that the polycystin block 2/cation channel domain is essential for LOV-1 activity and indicate that *lov-1(sy582Δ)* is completely defective in LOV-1 function.

- The *lov-1 (sy582)* mutant is a 1059 bp deletion of nucleotides 18026 to 16968 of ZK945 (nucleotides 2267 to 1209 of SEQ ID NO. 3). The deletion, which begins in exon W, removes the majority of the PKD homology block 2 (a total of 308 amino acids, beginning at amino acid 2520 and ending at amino acid 2827 of the sequence set forth in SEQ ID NO. 4) and continues to read in-frame to the end of the sequence set forth in SEQ ID NO. 4. This results in a protein of 2870 amino acids with the amino acid sequence set forth in SEQ ID NO. 15.

Other mutants may be prepared by any method known to those of skill in the art, including directed mutagenesis of the gene in a selected nematode or random mutagenesis and selection for the altered male mating behavior in the *lov* and/or response, preferably both behaviors.

- 5 Preferred regions for deletion include the exon A. Precise size of the deletion and or locations to delet can be determined empirically using standard routine methods based upon the disclosure herein, which identifies the gene and the resulting phenotype. Other mutations including insertions and point mutations that alter these behaviors are also
- 10 contemplated and can be readily prepared.

Expression patterns of *lov-1*

- To elucidate the cells in which *lov-1* acts to affect male mating behaviors, the expression pattern of *lov-1*::GFP reporter genes was examined (see Example 2 and Fig. 4). These experiments reveal
- 15 regulatory regions in the *lov-1* gene. A partial translational fusion containing 2.8 kb of upstream sequence and 3.9 kb of *lov-1* (*plov-1*::GFP1) directs male-specific expression in male-specific sensory neurons (Fig. 2c and Fig. 4). Conversely, shorter versions of *plov-1*::GFP1 are not expressed in the same set of male-specific neurons nor
- 20 exclusively in male-specific sensory neurons and do not act as DNAs (Fig. 2c). Similar results were observed with *pkd-2* mutants (see Example 2 and Fig. 4).

Nematode *pkd-2*

- A search for a homolog of *LOV-1* was performed to ascertain
- 25 whether nematodes possess a PKD2 ortholog. A BLAST search of the Sanger Center *C. elegans* genome data base revealed a possible *LOV-1* homolog, Y73F8A.B. This cosmid encodes a protein with 27% identity to PKD2 and possesses the coiled-coil domain of all polycystins. It is shown herein that Y73F8A.B and Y73F8A.A encode one transcript that is the *C. elegans* ortholog of human PKD2 (Fig. 2d and Fig 3). The resulting
- 30

nematode gene, designated *pkd-2*, cDNA and encoded protein are provided herein.

The *C. elegans* gene is exemplified herein. SEQ ID No. 5, which sets forth the complement of the coding strand, is provided. It contains
 5 nucleotides 1605 to 9677 of *C. elegans* cosmid Y73F8A (GenBank Accession No. AL132862), which correspond to nucleotides 1 to 8073 of SEQ ID No. 5. The sequence of the encoded protein is set forth in SEQ ID No. 6. Figure 3B shows *pkd-2* genomic structure (exons shown as boxes, introns as lines). The cDNA yk219e1 was sequenced and
 10 corresponds to the 3' end of *pkd-2*.

Figure 3B shows the *pkd-2* genomic structure (exons shown as boxes, introns as lines). The coding sequence in the gene set forth in SEQ ID No. 5 is produced as follows:

Complement (Join (7980...8073) - Exon 1; (7396...7585) - Exon 2;
 15 (6765...7045) - Exon 3; (5153...5283) - Exon 4; (4863...5104) - Exon 5; (3931...4158) - Exon 6; (2875...3424) - Exon 7; (1957...2208) - Exon 8; (1542...1795) - Exon 9; (367...505) - Exon 10; (1...87) - Exon 11.

As discussed above, the architecture of *LOV-1*, including a large extracellular amino terminus, Block 1, and Block 2, is similar to that of
 20 human PKD1; the architecture and sequence of *PKD-2* is similar to PKD2. Taken together, *LOV-1* and *PKD-2* appear to be part of a multi-component complex and pathway. Further genetic analysis of *Lov* behavior confirms this.

Knockout mutation of *pkd-2*

25 A knockout mutation can be prepared by any method known to those of skill in the art. A deletion mutant, designated *sy606* was produced (see, Examples for primers used). A 2397 bp deletion from nucleotides 8338 to 5942, starting in intron 3 and ending in intron 5, removing exons 4 and 5 (including the partial transmembrane spanning
 30 domain S1 and the polycystin motif) with the new splice in a different reading frame resulting in a stop codon (TGA) at 5736, produced a

knockout mutation. The resulting phenotype was the same as that resulting from a knockout of *lov-1*, thereby demonstrating that the two proteins are part of the same pathway that results in the observed phenotype.

- 5 The *pkd-2* (*sy606*) mutant contains a 2397 bp deletion of nucleotides 8338 to 5942 of Y73F8A (nucleotides 6734 to 4338 of SEQ ID NO. 5), starting in intron 3 and ending in intron 5, removing exons 4 and 5 (including the partial transmembrane spanning domain S1 and the polycystin motif) with the new splice in a different reading frame. This
- 10 results in a stop codon (TGA) at nucleotide 5728 (nucleotide 4124 in SEQ ID NO. 5). The sequence of the protein encoded by the *pkd-2* deletion mutant (*sy606*) is set forth in SEQ ID NO. 16.

TABLE 4
Comparison of Sequence ID No. 5 with source Cosmid

15	EXON	SEQ ID 5	Y73F8A
	1	7980..8073	9584..9677
	2	7396..7585	9000..9189
	3	6765..7045	8369..8649
	4	5153..5283	6757..6887
20	5	4863..5104	6467..6708
	6	3931..4158	5535..5762
	7	2875..3424	4479..5028
	8	1957..2208	3561..3812
	9	1542..1795	3146..3399
25	10	367..505	1971..2109
	11	1..87	1605..1691

- 30 **the *sy606* *pkd-2* mutant has a 2397 bp deletion of nucleotides 8338 to 5942 of Y73F8A (GenBank Accession No. AL132862; nucleotides 6734 to 4338 of SEQ ID NO. 5), starting in intron 3 and ending in intron 5, removing exons 4 and 5, with the new splice being in a different reading frame and resulting in a stop codon (TGA) at nucleotide 5728 (4124 in SEQ ID NO. 5).

Other such deletions may be similarly produced by deleting any portion that eliminates at least one of the observed phenotypic behaviors

associated with the *lov-1* and *pkd-2* pathway. Preferable targets for these deletions are those that destroy reading frame resulting in non-functional truncated proteins, deletions that eliminate transcriptional or translational control regions, deletions in the first exon or exon such that

5 the deletion (or insertion or point mutation) eliminates or substantially attenuates activity of the encoded protein as evidenced by altered phenotype.

The *lov-1* and *pkd-2* genes encode homologs of the polycystins

It is shown herein that the *lov-1* and *pkd-2* genes and gene

10 products are homologs of mammalian polycystins, particularly PKD1 and PKD2, respectively. As such nematodes that express these genes, and/or mutants of the genes can serve as models to study the expression of the genes, the function of these genes, to identify additional genes in the pathway, and for screening for compounds that will serve as lead

15 compounds for treatment of PKD in mammals, particularly humans.

Neither the precise functions of the polycystins nor the molecular basis of kidney cystogenesis is known. The results provided herein show that the homologs of the polycystins act together in a pathway, that appears to be a signal transduction pathway, in sensory neurons. It has

20 been postulated that human polycystin 1 and polycystin 2 function as an ion channel (Torres *et al.* (1998) *Current Opinion in Nephrology and Hypertension* 7:159-169). Further supporting this conclusion, are the results of others that have indicated that human PKD2 is associated with the activity of a cation channel. These results were obtained using cell-

25 expression and electrophysiological approaches to examine the potential channel function of a protein called PCL (polycystin-like) that had been identified in the human expressed sequence-tag database by its sequence similarity with PKD2 (Chen *et al.* (1999) *Nature* 401:383-386). PCL was expressed in *Xenopus oocytes* by microinjecting synthetic mRNA and the

30 channel properties were studied using the two micro-electrode voltage clamp and patch-clamp techniques. It was found that PCL is a non-

selective cation channel that is permable to sodium, potassium and calcium. It is more permeable to calcium. Thus, PCL and PKD2 may be cation-channel subunits.

- Hence, as shown herein, PKD1-related proteins act as receptors
 5 that regulate the activity PKD2-related proteins. The two proteins are part of a conserved pathway that appears to be a signalling mechanism in which the translocation of ions acts as a second messenger.

Exemplary strains

- Strains that exhibit one or more of the behaviors are provided. The
 10 strains may be prepared by mutagenizing wild-type or other strains with other desirable characteristics and selecting for those with the behavioral phenotype.

Strain PS3152 is an N2 strain with a deletion in *lov-1* (*lov-1(sy582)*)

- 15 Strain PS2816 has the *lov-1(sy552)* deletion in a background with a *him-5* (high incidence of males) and *plg-1*, which is a mutation that causes the male to use a gelatinous mating plug (which can be used to visualize mating).

Strain PS2817 is a paralyzed (*unc-52*) version of PS2816.

- 20 Strain PS3150 has the same deletion in a background with a *him-5* (high incidence of males) and *ts* lethal marker (*pha-1*). A strain with a *ts* marker is a good recipient for transformation.

strain recipient for transformation - *pha-1* marker - , any marker can be

PS3151 is the same as PS2815 without the *plg-1*

- 25 PS3149 has a *pha-1* marker, in a *him-5* background and and transformed with an extrachromosomal element containing a *lov-1::GFP1* construct and *pha-1(+)* DNA.

Another strain is an *him-5* strain with the *lov-1(sy582)* deletion.

PS3400 has a deletion mutation in *pkd-2*, it is *pkd-2(sy606)*.

- 30 PS3401 is a *him-5* strain with the *lov-1(sy582)* deletion
 PS3377 is *pkd02(sy606)* in a *him-5* background.

These and other strains may be used in the assay methods described herein or in any assay that assesses the pathways and sensory functions which *lov-1* and/or *pkd-2* are involved or that can be used for identifying compounds that affect this pathway(s).

5 Assays for screening compounds and for identifying mutants with observable Lov and/or response defective behavior

Assays for identifying additional genes in the pathway, to assess the activities of proteins in the pathway, to identify regulators of gene expressions and factors involved in gene expression of genes in this

- 10 pathway, and for screening for compounds that affect polycystin function are provided. Compounds that affect polycystin function in a nematode are candidates for further investigation and serve as leads for compounds that may be therapeutically useful for treating mammalian PKDs.

Identification of components of the PKD pathway will aid in

- 15 understanding the etiology of the disease and permit identification of disease markers and defective genes, thereby permitting development of reagents for diagnostic tests and identification of therapeutic targets and therapeutic agents.

The assays may be adapted for high throughput methods,

- 20 particularly by using multiwell plates, such as 24, 96, 384 wells or higher densities, and automating many of the steps. By using multiple wells, for example, many compounds can be screened. The results can be automated by using video or other recording means to record the behavior in each well. Viewing using such means is facilitated by visually labeling
- 25 the animals, such as by introduction of reporter gene constructs that will be expressed in areas of interest, such as the vulval and tail region of the hermaphrodite, to render the animal visible to a camera. If a GFP is used, for example, the camera will be equipped with an appropriate filter to screen out all but the green glow. Other ways of making the animals
- 30 visible, include, for example, use of *plg-1* animals, which leave a visible gelatinous trail as they move through the agar.

Precise protocols for culturing and nematodes, producing mutants and transgenics, and for observing behaviors are well known to those of skill in the art.

Assays using wild-type males

5 Behavioral screens

In these assays males will be identified that exhibit abnormal behavior, particularly abnormal Lov and/or response behaviors, thereby detecting components of PKD function, signaling or regulators, or identifying compounds that are candidates for affecting PKD function, signaling or regulation. A behavioral assay is depicted in Fig. 1, and described herein.

The tests are performed by placing male nematodes on an agar surface, such as a petri dish or microtiter plate with an agar surface, that is seeded with anything, including bacteria or chemoattractants, such as NaCl, that will keep the males in a field of view. One or more mating partners, such as a hermaphrodite, is placed on the plate and the behavior is recorded, such as by direct observation, review of a video tape, or any method whereby the behavior can be recorded.

For example, observations of the behaviors can be observed using young adult hermaphrodites, such as *unc-31(e169)* hermaphrodites, on a lawn of bacteria, such as *E. coli*. The use of *unc-31* hermaphrodites, which are sluggish, makes it easier for males to keep pace with them.

For drug screening assays, the effects of a test compound are examined. The males are treated with a compound, such as by culturing them in the presence of the compound., or including the compound in the mating dish, or pretreating the males with the compound. For analysis of mutants, males from parents or grandparents that had been mutagenized with chemical and/or radiation are tested.

In either embodiment, the behavior of the males is observed by looking for one or both, preferably both, of the Lov and 'response' behaviors compared to controls, untreated males for the drug screening

assays or wild-type for the mutant assays. If behavior of the treated males differs from controls, then the compound has some activity and is selected for further analysis.

- For the assays of mutants, if the behavior of the males differs from the controls, the mutation(s) are identified, such as by mapping. The mutant gene is then identified, genetically analyzed and its role in the pathway elucidated.

- These methods as well as the others provided herein can be adapted for high throughput analysis, including automation, such by videotaping and image processing. For image processing the animals can be visually labeled, such as by expressing, a reporter gene, like GFP, to produce stable transgenic strain of some construct of GFP with any promoter that would direct expression with sufficient intensity or in a sufficient number of cells to visualize the behavior. For example, a glowing vulva and tail would permit visualization of the Lov and response behaviors. Suitable genes for linkage to a reporter are any that are expressed in the animal to permit such visualization. Such markers include, but are not limited to, autofluorescence of the male spicule, *egl-5-gfp*, and of the hermaphrodite vulval region *lin-11-gfp*.

- Measurements can be performed by any method known to those of skill in the art (see, *e.g.*, Liu *et al.* (1995) *Neuron* 14:79-89). Briefly, measurements can be are obtained as follows: time is kept with a stopwatch or key stroke recorder on a computer to record an 'ethogram', and distances estimated by eye and confirmed from micrographs taken of the behavior. Mating behavior is sensitive to a number of variables, including the moisture level of the plates, which are not used if they are more than a week old, hermaphrodite age. Hence controls and test animals are carefully matched. At least three hermaphrodites are used per male to control for hermaphrodite specific behaviors.

Mating efficiency assays

As noted above, deletion of *lov-1* compromises but does not abolish the ability to mate. The mutant male can mate with paralyzed or moving impaired partners. To perform these assays, wild-type males are
 5 treated with a test compound or mutagenized, and males that sire fewer cross-progeny compared to wild-type or cannot sire cross-progeny with moving partners are identified.

To detect whether the progeny are those of the males rather than the hermaphrodites, sperm defective hermaphrodites can be used.
 10 Preferably the hermaphrodites are temperature-sensitive (*ts*) sperm defective. Alternatively, the mating can be detected by using a visual marker, such as using short and fat (*Dpy;Dumpy*) hermaphrodites, or males that express a visually or otherwise detectable transgene, such as fluorescent proteins (FPs), including, but not limited to blue fluorescent
 15 proteins and green fluorescent proteins (GFPs), and looking for the transgene in progeny could have a transgene transferred into the progeny by the mating and detectable. If a FP is used as a marker, glowing offspring are detected.

Progeny can also be detected by measuring the density of the
 20 resulting culture and a *ts* sperm defective hermaphrodite. If there are lot of progeny, it can be inferred that the males have mated, since the hermaphrodite is sperm defective.

Assays using mutant males

Suppressor and enhancer genetics can be used to assign functions
 25 to genes, to assign genes to pathways, to identify the key switches in these pathways and to provide a sensitive assay to identify new genes in a pathway and lead compounds that modulate the activity of genes and/or gene products in the pathway.

Suppressor screen

- In these assays, the process starts with a *lov-1* mutant and restoration of one or both behaviors is assessed, thereby identifying compounds or mutations that restore the defect. Restoration can occur, for example, by by-passing the defective gene, such as constitutive expression of a gene further down the pathway that had previously required *lov-1* or *pkd-2* activity. Alternatively, a mutation could knock-out the activity of another gene that suppresses the activity of *lov-1* or *pkd-2*, thereby restoring the pathway. These assays will identify other genes in the pathway. These assays can also identify a compound that corrects defect in the pathway, thereby providing a promising therapeutic lead for treatment of APKD.

Enhancer screen

- In these assays, the defect is exacerbated by looking for mutations or compounds that increase the penetrance of the phenotype caused by the *lov-1* or *pkd-2* mutations for either or both of the 'response' and Lov defect. This is achieved by screening for males that cannot sire cross progeny with paralyzed hermaphrodite mating partners or by observing the behavior directly. The genes with mutations responsible for the increased penetrance that differ are identified and those that are not *lov-1* or *pkd-2* are selected. Mammalian, particularly human, homologs of the selected genes are identified, and tested to assess their role in PKD diseases, such as, for example, by screening PKD patients for alterations in the homologous (or orthologous) gene, analysis of mouse model knockout mutations, or other methods known to those of skill in the art.

Assays for identifying the role of PKD proteins in sensory function

- As shown herein, *lov-1* and *pkd-2* are expressed in CEM neurons, indicating that they have activity in other sensory functions, such as finding a mating partner at a distance, *i.e.* sexual chemotaxis or kinesis, where the male randomly finds a hermaphrodite and then stays nearby. Hence sexual or chemoattraction assays can be used to study PKD function. To perform this assay, for example, put males that are

mutagenized or treated with a test compound on a surface containing at particular locations hermaphrodites and a control (*i.e.*, males, or other hermaphrodites, or buffer), The proportion of fraction of males that choose the hermaphrodites compared to the control is scored. If the male
 5 is defective in this sensory function, it will not distinguish between males and hermaphrodites.

Other sensory functions can be assessed to identify the role, if any, of PKD genes in the functions.

10 **Assays that use dominant negative forms of PKD in nematodes or in other cells to identify mutations and/or compounds that inhibit or otherwise alter PKD function**

Transgenic nematodes that express a version of the LOV-1 or PK2D protein that inhibits the activity of LOV-1 and/or PKD-2 as assessed by manifestation of the altered LOV and/or response phenotypic behavior(s)
 15 are used in these assays.

As described above, a dominant negative mutation is a mutation that encodes a polypeptide that when expressed disrupts that activity of the protein encoded by the wild-type gene (see, Herskowitz (1987) *Nature* 329:219-222). A cloned gene is altered so that it encodes a
 20 mutant product that upon expression in an organism or cell containing the wild-type gene, expression of the wild-type product is inhibited or eliminated. As a result, the cell or organism is deficient in the product. The mutation is "dominant" because its phenotype is manifested in the presence of the wild-type gene, and it is "negative" in the sense that it
 25 inactivates the wild-type gene function. It is possible to do this because proteins have multiple functional sites. Hence an assay that identifies a dominant negative mutation can identify functional activities of a protein.

In this instance, the assays use transgenic nematodes that contain such a dominant negative *lov-1* or *pkd-2* transgene. In certain assays,
 30 the transgenic mutants are mutagenized, and mutants that lose a remaining activity are selected. The mutations and genes responsible for

the loss are identified. Corresponding mammalian, particularly human, genes, such as by searching databases for homologs or by probing libraries with the nematode genes, are identified.

In the compounds screening assays that employ these transgenic
 5 nematodes, compounds that interfere with a remaining activity of the *lov-1* or *pkd-2* gene are identified. For example, as shown herein, *plov-1.3* (*plov-1.3* encodes a truncated protein lacking the polycystin block 2/channel domain) has a dominant negative effect in transgenic
 10 nematodes affecting only the Lov behavior, not Response. Compounds that rescue this dominant negative effect include those that interfere with the synthesis, binding or function of the amino-terminal region of the LOV-1 protein.

Since the dominant negative effect only affects the Lov response, a stable transgenic nematode strain that expresses a dominant negative of
 15 *lov-1*, can be used to screen for compounds and mutations that further affect Response well.

Assays based on localization and trafficking of LOV-1 and/or PKD-2 within a cell or cells

To identify regulators and factors necessary for synthesis and
 20 transport of *LOV-1* and/or *PKD-2* proteins, strains in which LOV-1 and PKD-2 are expressed linked to a detectable label, such as a fluorescent protein, can be and have been produced. It has been shown that these proteins are expressed in the ciliated endings and in the baso-dendritic compartment of HOB, ray neurons or CEM neurons.

25 These strains, such as PS3149, described above, can be used to study the trafficking patterns of *LOV-1* and *PKD-2* and cellular location(s) of the proteins in the animal by looking for mutants thereof that have altered trafficking and/or altered localization of one or both of these proteins. The mutations can be mapped, genetically analyzed and the
 30 genes identified. Such genes could serve as therapeutic or diagnostic targets.

Assays for identification of transcriptional regulators of expression of *lov-1* and/or *pkd-2*

To identify transcriptional regulators of *lov-1* or *pkd-2*, a screen for loss or alteration of expression of either gene is provided.

- 5 Transgenic nematodes with a reporter gene, such as a gene encoding a FP or lacZ or other detectable product, linked to the nucleic acid encoding *lov-1* or *pkd-2* is used. The animal is mutagenized or treated with a test compound and loss of expression or reduction in expression of either gene is assessed by detecting, such as by observing under a dissecting or
- 10 compound microscope or other means, including whole animal sorting, the number of cells that express the detectable marker, such as a FP.

As a control, to avoid detection or identification of non-specific effects, an unrelated gene, such as *lin-3*, linked to a reporter, is expressed in other cells in these animals. Only mutants that exhibit changes in

- 15 expression of *lov-1* or *pkd-2*, but not expression of the other gene, are selected for identification and mapping of the mutation. If expression of the other gene is affected also, then mutation is likely affecting a general process and would not be of interest.

- 20 These assays will identify regulators of and factors that affect *lov-1* and *pkd-2* expression, which regulators and factors could serve as therapeutic or diagnostic targets, or which can aid in developing an understanding of the development and progression of PKD in mammals.

Visual screen based on clumping behavior

- 25 Wild type adult males isolated from hermaphrodites will clump together on a plate with a lawn of bacteria. In contrast, *lov-1* and *pkd-2* mutant males do not exhibit this clumping behavior. Rather, *lov-1* and *pkd-2* mutant males are randomly dispersed in the bacterial lawn. This assay may be used for a variety of purposes, including, but not limited to, the identification of compounds that inhibit wild type male clumping
- 30 behavior, compounds that restore clumping behavior to *lov-1* or *pkd-2*

mutants, and the identification of genetic suppressors of *lov-1* or *pkd-2* mutants.

Kits and diagnostic systems for performing the assays

Kits for use in screening for use in any of the assays are provided.

- 5 The kits include transgenic or wild-type nematodes or both that express either wild-type or a mutant or a transgenic form of *lov-1* and/or *pkd-2*. The nematodes may be on plates, in wells or in any form suitable for the assays. Kits containing nucleic acid encoding either of the two genes, portions thereof or vectors or plasmids containing the nucleic acids
- 10 or probes based upon these sequences or reporter gene constructs containing all or portions of either or both genes and a reporter molecule are also provided. The nucleic acids may be in solution, in lyophilized or other concentrated form, or may be bound to a suitable substrate. The kits can include additional reagents for performing the assays, such
- 15 reagents include any for performing any of the steps of the methods. The kits include instructions for performing the assays.

- 20 The kits may also include suitable ancillary reagents, such as the appropriate buffers and reagents. The kits may also include suitable ancillary supplies, such as microtiter plates, vials, calibrator solutions, controls, wash solutions and solid-phase supports.

- 25 The kits are typically provided in packages customarily utilized in diagnostic assays. Such packages include glass and plastic, such as polyethylene, polypropylene and polycarbonate, bottles and vials, plastic and plastic-foil laminated envelopes and the like. The packages may also include containers appropriate for use in auto analyzers. The packages typically include instructions for performing the assays.

The following examples are included for illustrative purposes only and are not intended to limit the scope of the invention.

EXAMPLE 1

Identification of *C. elegans* orthologs of human polycystins

Mating behavior and mating efficiency assays. Males were generated by use of *him-5(e1490)* (high incidence of male) strains or by
 5 heatshock of L4 hermaphrodites (Brenner (1974) *Genetics* 77:71-94). Mating efficiency (ME) tests were performed by pairing six tester L4 males with six paralyzed *unc-52* or four actively moving *dpy-17* or N2 L4 hermaphrodites. ME is the percentage of cross progeny to total progeny (Hodgkin (1983) *Genetics* 103:43-64). Behavioral observations were
 10 done on a 0.5 cm diameter lawn of OP50 (Liu *et al.* *Neuron* 14:79-89). Hermaphrodites (N2 or *unc-31(e169)*) were placed on a lawn with the tester male. Behavioral phenotypes were determined by keeping time with a stopwatch and manually recording the behavioral series. In one trial, a male is observed for a minimum of 10 vulva encounters or for 10
 15 minutes, whichever comes first. A male who does not respond to hermaphrodite contact within 10 minutes is considered response defective. Response ability reflects the percentage of males successfully responding to hermaphrodite contact. An individual male's vulva location ability was calculated as: Number of positive vulva locations/Total number
 20 of vulva encounters. Ability can vary from 100% (always locate) to 0% (never locate). Vulva location efficiency indicates the average behavior of a genotypic population. Pairwise comparisons were made using Mann-Whitney nonparametric and two-sided t tests (Instat for MacIntosh).

Genetic screen for location of vulva (Lov mutants). PS1395
 25 hermaphrodites of genotype *plg-1(e2001d); him-5(e1490)* were mutagenized with EMS (Brenner (1974) *Genetics* 77:71-94). *plg-1(e2001d); him-5(e1490)* males deposit a gelatinous plug over the hermaphrodite vulva post coitum. A decrease in plugging efficiency might reflect a decrease in mating ability. An F1 clonal screen was performed
 30 by picking individual F1 progeny of mutagenized hermaphrodites to individual plates and directly observing F2 males for behavioral defects.

An F2 clonal screen was performed such that 10 F1 progeny per PO hermaphrodite were picked to the same plate, 10 F2 hermaphrodites per F1 pool were picked to individual plates, and F3 males were observed for decreased plugging efficiency and/or location of vulva (Lov) defects. *lov-*
 5 *1(sy552); plg-1(e2001d); him-5* is a recessive mutation isolated in the F2 clonal screen. *lov-1(sy552)* males are response and Lov defective and also have a very low ME with *dpy-17* hermaphrodites (ME-Dpy).

Genetic mapping of *lov-1*. Chromosomal linkage of *lov-1(sy552)* was determined by scoring the loss of genetic markers relative to
 10 response, Lov, and ME-Dpy phenotypes, which revealed linkage between *dpy-10* and *sy552*. Further mapping was achieved via three factor crosses. From *sy552/unc-4(e120) let-25(mn25)* heterozygotes, Unc non-Let (Unc for uncoordinated, Let for lethal) recombinants were picked. As Unc males cannot mate, a test cross with *sy552* males and Unc
 15 hermaphrodites was performed to generate non-Unc *sy552/(sy552Δ)unc-25(mn25)* males. Males were scored for response, Lov, and ME-Dpy defects. 2/12 Unc non-Let recombinants segregate the *lov-1* mutant phenotype. These data placed *lov-1* between *unc-4* and *let-25*, closer to *unc-4*. Deficiency mapping indicated that *mnDf21* uncovers *sy552*
 20 whereas *eDf21* does not.

Transformation rescue of *lov-1(sy552)* mutants. Cosmids and plasmids (15-100 ng/μl) in the region from the right breakpoint of *eDf21* to the right breakpoint of *mnDf21* and PHA-1 (pBX, 100 ng/μl) were injected into *lov-1(sy552); pha-1(e2123ts); htm-5(e1490)*. Stable lines
 25 were selected at either 19° or 25°C (Schnabel *et al.* (1990) *Science* 250:686-688). Cosmid ZK945 rescued *sy552* response and vulva location defects in four of five stable lines. A 16.9 kb HindIII fragment of ZK945 cloned into pBS(SK+) (plov1.1) containing ORFs ZK945.10 and ZK945.9 rescued *sy552* behavioral defects in 4 of 6 stable lines. A 6.7
 30 kb HindIII-BamHI fragment of ZK945 (plov-1::GFP1) containing ORF ZK945.10 did not rescue *sy552* defects. plov-1.3 creates a frameshift at

nucleotide 17724 in ZK945 inserting a BssHII GFP fragment from plasmid pPD95.02 out of frame into the StuI site of *plov-1.1* *plov-1.3* fails to rescue *sy552*.

PCR screen for genomic deletion of *lov-1*. Approximately 315,000

- 5 haploid genomes were screened using primers designed to delete the PKD/channel domain. Primer set 1 (SEQ ID Nos. 7 and 8, respectively), the outside primers were:

JC32 5'-CTCTATTTGTGGTTCGTTGGCG-3' and

JC36 5'-GGGAGTTTCCGTTTTTCATGGGG-3'; and

- 10 internal nested primer set (SEQ ID Nos. 9 and 10, respectively) were:

JC33 5'-CTAGGACCGATGCAACAGCGAG-3' and

JC35 5'-AACGCTGATTGGTTCAAGTGTG-3')

are approximately 2.5 and 2.4 kb apart, respectively. One deletion allele, *lov-1(sy582Δ)* was isolated. DNA sequence analysis indicated a deletion

- 15 of nucleotides 16972 to 18027 of ZK945.

DNA-sequence analysis. RT-PCR from *him-5(e1490)* RNA using a combination of *lov-1* primers generated overlapping cDNA clones bridging the junction between ZK945.10 and ZK945.9. Genefinder had predicted boundaries of the last exon of ZK945.10 (from position 25742 to 25174 of ZK945) and first exon of ZK945.9 (24923 to 24444). DNA sequence analysis of RT-PCR generated cDNA clones revealed three exons in the junction: one from 25742 to 25195, a second from 25151 to 25071, and a third initiating a position 25021, corresponding to exons I, J, and K, in Fig. 2b, respectively.

- 25 **PCR screen for genomic deletion of *pkd-2***

For *pkd-2* the used primers (SEQ ID Nos. 11-14, respectively) were as follows:

Outside primers

LOV2.9 (Y73F8A nt 8546-8569) 5' CCCCTCGTTTGACCATTCTATGG 3'

- 30 LOV2.10 (Y73F8A nt 8438-8457) 5' ACGTGATCCTCTGTCGATCCAG 3'

Nested Primers

LOV2.9A(Y73F8A nt 5599-5615) 5' AGATCAAGCTGACTGCCCCGTTC 3'
 LOV2.10A(Y73F8A nt 5609-5631) 5'GATCCAGCGATTAGCCTTTAA CG3'/

- One deletion allele, *pkd-2(sy606)* was isolated, which has a 2397 bp deletion from nucleotides 8338 to 5942 of Y73F8A (GenBank Accession
- 5 No. AL132862; corresponding to nucleotides 6734 to 4338 of SEQ ID NO. 5). The deletion starts in intron 3 and ends in intron 5, removing exons 4 and 5 (including the partial transmembrane spanning domain S1 and the polycystin motif) with the new splice in a different reading frame resulting in a stop codon (TGA) at 5736, produced a knockout mutation.
- 10 The resulting phenotype was the same as that resulting from a knockout of *lov-1*, thereby demonstrating that the two proteins are part of the same pathway that results in the observed phenotype.

EXAMPLE 2

Expression analyses of LOV-1 and PKD-2

15 Methods

- GFP (see, Chalfie *et al.* (1994) *Science* 263:802-805) expression was used a marker for *lov-1* and *pkd-2* gene expression (see Figs. 3a and 4A) plov-1::GFP1 was constructed by cloning a 6.7 kb *HindIII-BamHI* fragment of plov-1.1 into the vector pPD95.81, plov-1::GFP2 by cloning a
- 20 *HindIII-HpaI* fragment. plov-1::GFP3 and plov-1::GFP4 are *SacI* and *HindIII-HpaI* (Klenow filled-in and religated) deletions of plov-1::GFP1, respectively. plov-1::GFP5 was constructed by cloning a 15.4 kb *HindIII-AfeI* fragment of plov-1.1 into the *HindIII-SmaI* site of pPD95.79. ppkd-2.1, ppkd-2::gfp1 and ppkd-2::gfp2 were constructed by cloning PCR-
- 25 amplified 8.9 kb, 2.0 kb and 5.9 kb fragments into the vectors pPD95.97, pPD95.75 and pPD95.77, respectively. Transgenic animals were observed by fluorescence microscopy Cells were identified by comparing Nomarski and fluorescent or confocal images of the same animals to determine cell-body position (Sulston *et al.* (1980) *Dev. Biol.*
- 30 78:542-576). HOB assignment was confirmed by laser ablation of precursor cells.

lov-1 expression

lov-1::GFP1 is specifically expressed in male-sensory neurons, including four putative chemosensory CEM cephalic neurons, the hook neuron HOB (Fig. 4a), and the sensory ray neurons (Fig. 4b). *lov-1::GFP1* expression was first observed in a few cells during late L4 lethargus (data not shown) while strong expression peaks in the adult male. In neuronal cell bodies, GFP expression is cytoplasmic (non-nuclear) and punctate (Fig. 4a and Fig. 4b). *lov-1::GFP1* is localized at high levels in the cell body and ciliated endings of CEM (Fig. 4c), HOB, and ray neurons (Fig. 4b) but is not observed in axons. Localization of *lov-1::GFP1* to sensory endings is consistent with plasma membrane localization and strengthens the argument that *lov-1* mediates sensory perception required for mating behaviors. The temporal and spatial regulation of *lov-1* is concordant with its role in adult male mating behavior. Rays mediate response to contact with a hermaphrodite (Liu *et al. Neuron* 14:79-89), the hook mediates vulva location (Liu *et al. Neuron* 14:79-89), and the CEMs are postulated to play a role in chemosensation (Ward *et al. (1975) J. Comp. Neurol.* 160:313-337).

lov-1::GFP1 expression was unaltered in *lov-1(sy552)* mutants. Expression of this fusion gene did not rescue *lov-1(sy552)* defects (Fig. 2a) and is therefore not functional. Sensory neurons and structures are normal in *lov-1(sy552)* mutants as determined by *osm-6::gfp* expression, dye filling of sensory neurons, Nomarski observation, and SEM imaging (data not shown). The defects of *lov-1(sy552)* mutants therefore cannot be attributed to abnormal development or differentiation of the response and vulva location neurons. This indicates that *lov-1(sy552)* defects are due to defects in the function of the cells required for response and vulva location.

The Lov defect of mutations in *lov-1* is not identical to ablation of HOB, the chemosensory neuron in which *lov-1* expressed. The *lov-1* mutant and HOB-ablated males pass the vulva (Fig. 1). The *lov-1* males,

however, are capable of precisely locating the vulva, whereas HOB-ablated males resort to slow search. Therefore, the HOB neuron of *lov-1* functions, albeit in an attenuated capacity. If *lov-1(sy552)* and *lov-1(sy582Δ)* are loss of function alleles as the data suggests, then

5 additional components are involved in Lov sensation.

Chemosensation and mechanosensation are likely involved in Lov
C. elegans sensory neurons can be polymodal: for example, by
 ultrastructural assignment, the ASH neuron appears to be chemosensory
 yet functions in both mechanosensory (nose touch) and chemosensory
 10 (osmotic avoidance) modalities (Kaplan *et al.* (1993) *Proc. Natl. Acad. Sci. U.S.A.* 90:2227-2231). HOB might similarly be a polymodal sensory
 neuron. Ablation of either HOA or HOB produces identical phenotypes
 (Liu *et al. Neuron* 14:79-89) and HOA and HOB form multiple chemical
 synapses and electrical junctions (Sulston *et al.* (1980) *Dev. Biol.* 78:542-
 15 576), indicating extensive cross talk between the two hook sensory
 neurons. Since LOV-1 has an extensive extracellular mucin-like domain
 that could be involved in cell-cell or cell-matrix interaction, binding of
 vulva cell ligand(s) might potentially gate the LOV-1 polycystin-related
 channel. Another possibility is that LOV-1 could physically link the HOB
 20 sensory endings to the sclerotized hook structure and couple hook
 deflection by the hermaphrodite vulva to intracellular voltage-activated
 signaling similar to hair cell mechanosensation (Hudspeth (1989) *Nature*
 341:397-404) or touch response in *C. elegans* (Driscoll *et al.* in *C.*
elegans II (ed. Riddle, D.I., Blumenthal, T., Meyer, B.J., and Priess, J.R.)
 25 645-677 (Cold Spring Harbor Laboratory Press, New York, 1997).

pkd-2 expression

As shown herein, *C. elegans* genome contains a human PKD-2
 homolog. PKD-2 possesses six membrane-spanning domains, a positively
 charged fourth membrane-spanning segment, a pore region, and the
 30 coiled coil domain of all polysystins. PKD-2 is localized to the same male-
 specific sensory neurons as LOV-1 (see, Fig. 3 and Fig. 4).

Since modifications will be apparent to those of skill in this art, it is intended that this invention be limited only by the scope of the appended claims.

SEQUENCE LISTING SUMMARY

SEQ ID No. 1 cDNA encoding human PKD1

SEQ ID No. 2 encoded human PKD1 protein

SEQ ID No. 3 sequence of a gene encoding nematode LOV-1 protein

5 SEQ ID No. 4 encoded nematode *LOV-1* protein

SEQ ID No. 5 sequence of a gene encoding a nematode *PKD-2* protein

SEQ ID No. 6 encoded nematode *PKD-2* protein

SEQ ID No. 7 primer for *lov-1* deletion mutant construction

SEQ ID No 8 primer for *lov-1* deletion mutant construction

10 SEQ ID No. 9 internal primer for *lov-1* deletion mutant construction

SEQ ID No. 10 internal primer for *lov-1* deletion mutant construction

SEQ ID No. 11 primer for *pk2-1* deletion mutant construction

SEQ ID No. 12 primer for *pk2-1* deletion mutant construction

SEQ ID No. 13 internal primer for *pk2-1* deletion mutant construction

15 SEQ ID No. 14 internal primer for *pk2-1* deletion mutant construction

SEQ ID No. 15 sets forth the a *LOV-1* mutant protein from *sy582*

SEQ ID No. 16 sets a *PKD-2* mutant protein from *sy606*

CLAIMS:

1. An isolated nucleic acid molecule, comprising:
 - a) a sequence of nucleotides that encodes the sequence of amino acids encoded by one or more of the exons that is the complement
 - 5 of the sequence of nucleotides set forth in SEQ ID No.5; or
 - b) the sequence of nucleotides set forth as one or more of the exons that is the complement of the sequence of nucleotides set forth in SEQ ID No. in SEQ ID No. 5;
 - c) a sequence of nucleotides that hybridizes along its full
 - 10 length to the full length of at least one of the exons of SEQ ID No. 5 under conditions of at least moderate stringency, and that is present in the genome of a nematode; or
 - d) a sequence of nucleotides degenerate with the sequence of nucleotides of c).
- 15 2. An isolated nucleic acid molecule of claim 1, that encodes a PKD-2 protein from a nematode.
3. The isolated molecule of claim 1 that comprises a sequence of nucleotides that encodes the amino acids set forth in SEQ ID No. 6.
4. The isolated nucleic acid molecule of claim 1, wherein the
- 20 nematode is *Caenorhabditis elegans*.
5. An isolated gene, comprising the nucleic acid molecule of claim 1.
- 6 The gene of claim 5, wherein the gene comprises transcriptional control sequences that are homologous to the encoded
- 25 gene.
- 7 The gene of claim 5, wherein the gene comprises transcriptional control sequences that are heterologous to the encoded gene.

8. An isolated nucleic acid molecule that encodes a mutant of the protein encoded by the nucleic acid molecule of claim 2.

9. The nucleic acid molecule of claim 8, wherein the mutant is a deletion mutant, insertional mutant or comprises a point mutation.

5 10. The nucleic acid molecule of claim 8, wherein the encoded protein is inactive.

11. A construct, comprising a nucleic acid molecule of claim 1 operatively linked to a reporter gene.

10 12. The construct of claim 11, wherein the reporter gene encodes a fluorescent protein.

13. A plasmid, comprising a nucleic acid molecule of claim 1.

14. The plasmid of claim 13 that is an expression vector.

15. A transgenic nematode, comprising the vector of claim 14.

15 16. The transgenic nematode of claim 15, wherein in the vector is maintained extrachromosomally.

17. The transgenic nematode of claim 15, wherein in the vector or the gene-encoding portion is integrated into the *C. elegans* genome.

18. The transgenic nematode of claim 15, wherein the vector further comprises nucleic acid encoding a reporter gene operatively linked
20 to the nucleic acid molecule.

19. The transgenic nematode of claim 15, wherein the nucleic acid molecule encodes a mutant protein.

20. The transgenic nematode of claim 18, wherein the nucleic acid molecule encodes a mutant protein.

25 21. An isolated nucleic acid molecule, comprising a sequence of nucleotides encoding a mutant PKD-2 protein, wherein a nematode that expresses such defect exhibits one or both of an altered Lov and response phenotype, and the PKD-2 protein is encoded by the nucleic acid molecule of claim 1.

22. A transgenic nematode, comprising the nucleic acid molecule of claim 21.

23. An isolated polypeptide encoded by the nucleic acid molecule of claim 1.

5 24. The polypeptide of claim 23 that comprises the sequence of amino acids set forth in SEQ ID No. 6.

25. An isolated nucleic acid molecule of claim 9, comprising a sequence of nucleotides that encodes the sequence of amino acids set forth in SEQ ID No. 16.

10 26. An isolated complex, comprising a nematode PKD-2 protein and a nematode LOV-1 protein in operative linkage.

27. A method, comprising:

introducing a mutation into the *lov-1* and/or *pkd-2* gene of a nematode, and

15 selecting nematodes that exhibit altered mating behavior, wherein the altered behavior includes a change in the ability to locate the vulva (Lov) of a hermaphrodite or a change in the response of the male to contact with the hermaphrodite (Response).

20 28. The method of claim 27, wherein the altered behavior is a change in the response of the male to contact with the hermaphrodite.

29. The method of claim 28, wherein the mutation is in the *pkd-2* gene.

30. The method of claim 27, wherein the nematode is a species of *Caenorhabditis*.

25 31. A method, comprising:
treating nematodes with a test compound or with a mutagenizing agent or treatment; and

selecting from among the nematodes or offspring thereof, nematodes that exhibit altered mating behavior compared to prior to the treatment; where the altered behavior includes one or both of location of vulva (Lov) or response of the male to contact with the hermaphrodite

5 (Response).

32. The method of claim 31, wherein prior to treatment the nematodes had exhibited normal mating behavior.

33. The method of claim 31, wherein prior to treatment the nematodes had exhibited defects in mating behavior, wherein the defects

10 were manifested as a defect in one or both of Lov and Response, and the alteration comprises a partial restoration or complete restoration of one or both of Lov and Response behaviors.

34. A method for identifying compounds, comprising:

contacting nematodes with a test compound;

15 selecting test compounds that result in altered mating behavior, wherein:

the altered mating behavior comprises alteration in the behavior involving location of vulva and/or response to contact with the hermaphrodite; and

20 the selected test compounds are candidates for treatment of polycystic kidney diseases of mammals.

35. The method of claim 34, wherein prior to treatment the nematodes had exhibited normal mating behavior.

36. The method of claim 34, wherein prior to treatment the

25 nematodes had exhibited defects in mating behavior, wherein the defects were manifested as a defect in one or both of Lov and Response, and the alteration comprises a partial restoration or complete restoration of one or both of Lov and Response behaviors.

37. The method of claim 34, wherein the selected compounds are candidate therapeutic agents for treatment of autosomal dominant polycystic kidney disease (ADPKD) or other diseases involving PKD1 or PKD2.

5 38. The method of claim 34, wherein prior to treatment the nematodes had defects in mating behavior, and the candidate compounds restore or partially restore either or both Lov and Response.

39. A method for identifying genes that are part of the disease pathway of autosomal dominant polycystic kidney disease (ADPKD),
 10 comprising:
 mutagenizing nematodes that exhibit normal mating behavior; and
 identifying and selecting nematodes or the male offspring thereof that exhibit altered mating behavior, wherein the altered mating behavior comprises alteration in the behavior involving location of vulva (LOV)
 15 and/or response to contact with the hermaphrodite (Response), thereby identifying nematodes that contain defects in genes in the pathway that comprises the *lov-1* and/or *pkd-2* gene(s).

40. The method of claim 39, further comprising, mapping the mutation(s) in selected nematodes that results in the altered behavior.

20 41. The method of claim 40, further comprising, identifying mammalian homologs or orthologs of the nematode genes to which the mutation is mapped.

42. A method for identifying compounds that are candidate therapeutic agents for treatment of autosomal dominant polycystic kidney
 25 disease (ADPKD), comprising:

treating male nematodes that can sire cross-progeny with moving partners with a test compound; and

selecting compounds that result in males that sire fewer cross progeny or cannot sire cross-progeny with moving partners, wherein the
 30 selected compounds are candidate therapeutic agents for treatment of ADPKD or diseases involving PKD1 or PKD2.

43. A method for identifying genes that are part of the disease pathway of autosomal dominant polycystic kidney disease (ADPKD), comprising:

- mutagenizing males nematodes that can sire cross-progeny with
- 5 moving partners with a test compound;
- selecting males or the offspring thereof that sire fewer cross-progeny with moving partners; and
- identifying the mutant nematode genes.

44. The method of claim 43, further comprising identifying

10 mammalian homologs of the genes that comprise the mutant nematode genes.

45. A method for identifying genes or regulatory factors involved in polycystic kidney diseases, comprising:

- mutagenizing nematodes that exhibit altered mating behaviors
- 15 because of a mutation in the *lov-1* or *pkd-2* gene;
- selecting nematodes or the offspring thereof that exhibit a restoration of the behavior associated with the wild-type gene; and
- identifying a second gene other than *lov-1* or *pkd-2* or a factor that results in restoration of the behavior, wherein restoration of the behavior
- 20 is a partial or complete restoration compared to prior to mutagenesis.

46. The method of 45, further comprising:

- identifying a mammalian gene that is orthologous to the second gene.

47. A method for screening compounds to identify candidates for

25 treatment of polycystic kidney diseases, comprising:

- contacting nematodes that exhibit altered mating behaviors because of a mutation in the *lov-1* or *pkd-2* gene with a test compound;
- and

selecting compounds that result in restoration of the behavior,

30 wherein restoration of the behavior is a partial or complete restoration compared to prior to contacting.

48. A method for identifying genes or regulatory factors involved in polycystic kidney diseases, comprising:

mutagenizing nematodes that exhibit altered mating behaviors because of a mutation in the *lov-1* or *pkd-2* gene;

- 5 selecting nematodes or offspring thereof that cannot sire cross progeny or sire fewer cross progeny with paralyzed hermaphrodite mating partners; and

identifying a gene responsible for the inability to sire cross progeny with paralyzed hermaphrodite mating partners.

- 10 49. The method of claim 48, further comprising identifying mammalian homologs of the gene responsible for the inability to sire cross progeny with paralyzed hermaphrodite mating partners.

50. A method for identifying genes or regulatory factors involved in polycystic kidney diseases, comprising:

- 15 mutagenizing transgenic nematodes that contain a dominant negative *lov-1* or *pkd-2* transgene;

selecting nematodes or offspring thereof that exhibit a further loss in function of the *lov-1* or *pkd-2* transgene by observing mating behaviors; and

- 20 identifying the mutations and genes responsible for the loss.

51. The method of claim 50, further comprising identifying homologous mammalian genes.

52. A method for identifying regulators and factors necessary for synthesis and transport of *LOV-1* or *PKD-2* protein;

- 25 preparing a transgenic nematode that expresses a detectable marker linked to *LOV-1* or *PKD-2* protein;

mutagenizing the nematode;

selecting nematodes or offspring thereof that have altered patterns of expression of *LOV-1* or *PKD-2*; and

- 30 identifying the gene responsible for the alteration.

53. A method for identifying transcriptional regulators of *lov-1* or *pkd-2*; comprising:

preparing a transgenic nematode that expresses a detectable marker linked to *LOV-1* or *PKD-2* protein;

5 mutagenizing the nematode;

selecting nematodes or offspring thereof that altered levels of expression of the protein.

54. A method, comprising:

10 treating nematodes with a test compound or mutagenizing them;

selecting nematodes or the offspring thereof that exhibit altered clumping behavior when seeded on a lawn of bacteria, wherein:

an alteration in the behavior is indicative of change in the genotype of the *lov-1* or *pkd-2* locus;

15 the wild-type males exhibit clumping behavior, and a males with a mutation in either locus that alters activity of either the *LOV-1* or *PKD-2* protein results in males that are randomly dispersed in the bacterial lawn.

55. The method of claim 54, wherein:

20 the nematodes are mutant nematodes that are randomly dispersed in the bacterial lawn and are treated with a test compound; and the method further comprises:

identifying compounds that restore or partially restore clumping behavior.

56. The method of claim 54, wherein the mutant nematodes 25 comprise males that are *pkd-2* mutants.

57. The method of claim 54, wherein:

the nematodes are mutant nematodes that are randomly dispersed in the bacterial lawn and then mutagenized; and the method further comprises:

selecting males or the offspring thereof that exhibit a partial or complete restoration of the behavior;
 analyzing the mutations; and
 identifying the genes or mutations responsible for the restoration.

5 58. (Amended) The method of claim 57, wherein the genes or mutations are genetic suppressors of *lov-1* or *pkd-2* mutants.

59. (Amended) The method of claim 57, wherein the mutant nematodes comprise males that are *pkd-2* mutants.

60. The method of claim 54, wherein:
 10 the nematodes are wild-type nematodes that are clumped in the bacterial lawn and are treated with a test compound; and the method further comprises:

identifying compounds that destroy the clumping behavior.

61. The method of claim 54, wherein:
 15 the nematodes are wild-type nematodes that are clumped in the bacterial lawn and then mutagenized; and the method further comprises:
 selecting males or the offspring thereof that are randomly dispersed on the bacterial lawn;

analyzing mutations responsible for the altered behavior; and
 20 identifying the mutant genes.

62. A mutant strain of nematode that comprises a mutation in the *pkd-2* gene, whereby the resulting nematode exhibits altered mating behavior compared to the wild-type, wherein the alteration is manifested as either or both a defect in behavior involving location of vulva (LOV)
 25 and response to contact with the hermaphrodite (Response).

63. The mutant strain of claim 62, wherein the mutation is in the *pkd-2* gene, wherein the wild-type *pkd-2* gene comprises:

a) a sequence of nucleotides that encodes the sequence of amino acids encoded by one or more of the exons that is the complement
 30 of the sequence of nucleotides set forth in SEQ ID No.5; or

b) the sequence of nucleotides set forth as one or more of the exons that is the complement of the sequence of nucleotides set forth in SEQ ID No. in SEQ ID No. 5;

- 5 c) a sequence of nucleotides that hybridizes along its full length to the full length of at least one of the exons of SEQ ID No. 5 under conditions of at least moderate stringency, and that is present in the genome of a nematode; or

d) a sequence of nucleotides degenerate with the sequence of nucleotides of c).

ABSTRACT

Nematodes, such as *Caenorhabditis elegans*, that express mutant and wild-type orthologs of human genes involved in polycystic kidney diseases (PKDs), are used to study the functions of the proteins encoded
5 by the genes, to screen for other genes involved in the diseases, to identify mutations involved in the diseases, and to screen for drugs that affect PKD. Behaviors controlled by the action of the genes or gene products are identified and used in the assays. Hence an animal model is provided that permits study of the etiology of polycystic kidney disease
10 and provides a tool to identify the genes involved in the disease pathway, and to identify compounds that may be used to treat or alter the disease progression, lessen its severity or ameliorate symptoms. The nematode genes that encode protein products, mutants of the genes, vectors contain the genes and mutant genes and nematode strains that contain
15 the vectors are also provided.

003060:091660

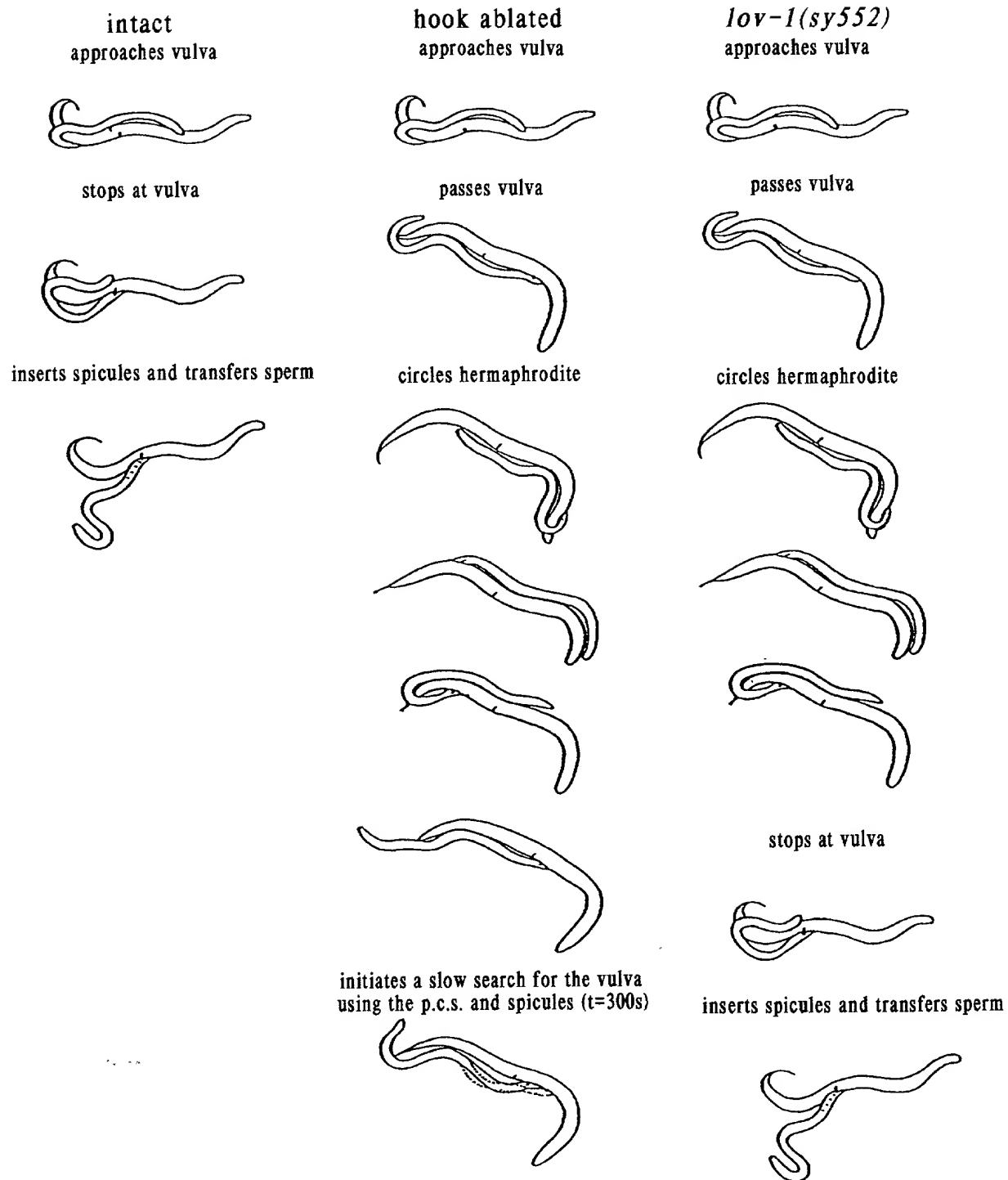


FIG. 1

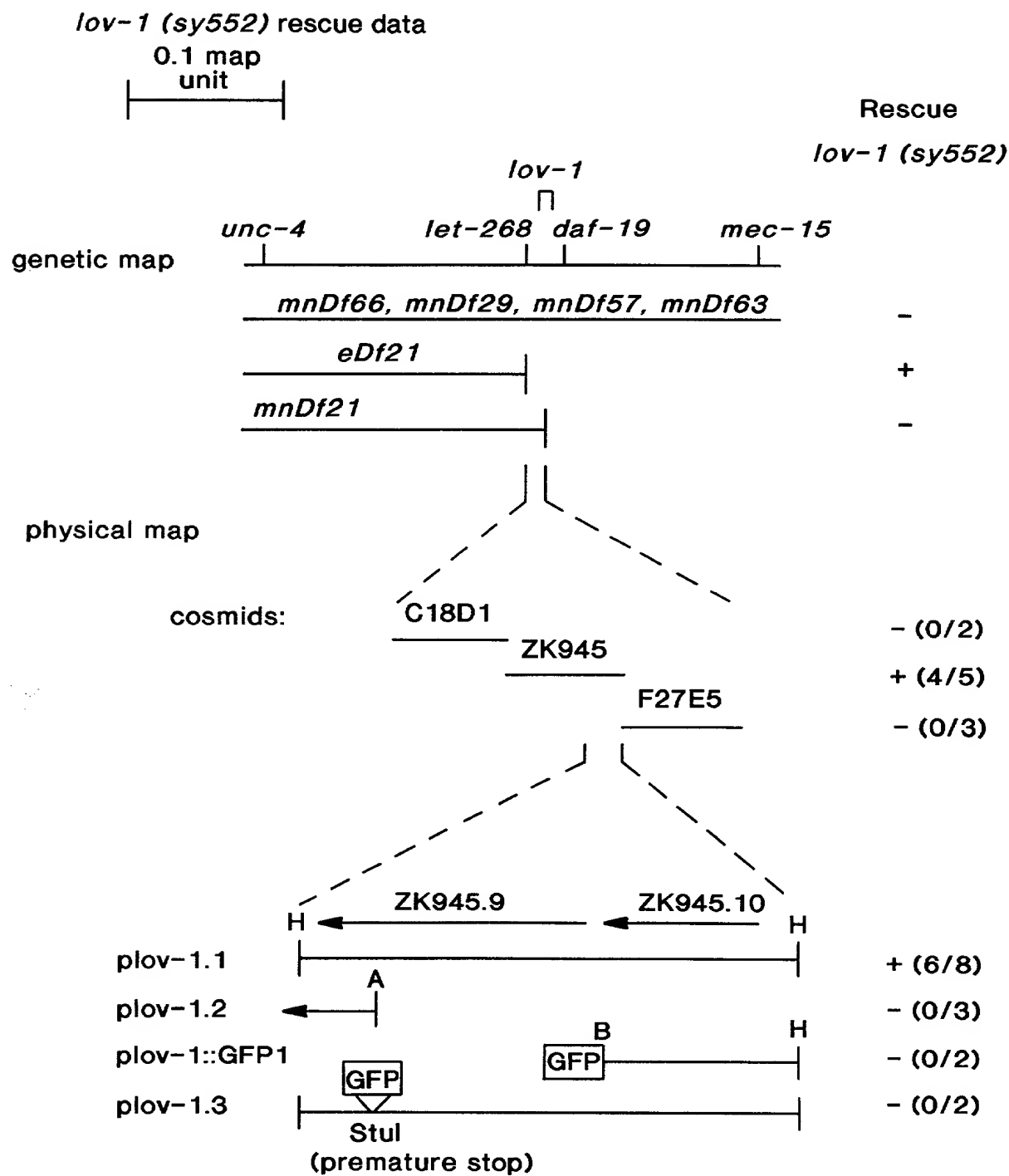


FIG. 2A

Schematic of GFP fusion constructs and expression data

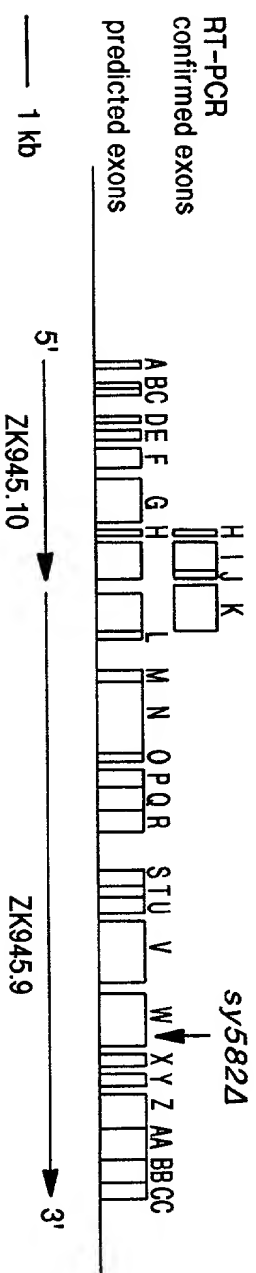


FIG. 2B

Schematic of GFP fusion constructs and expression data

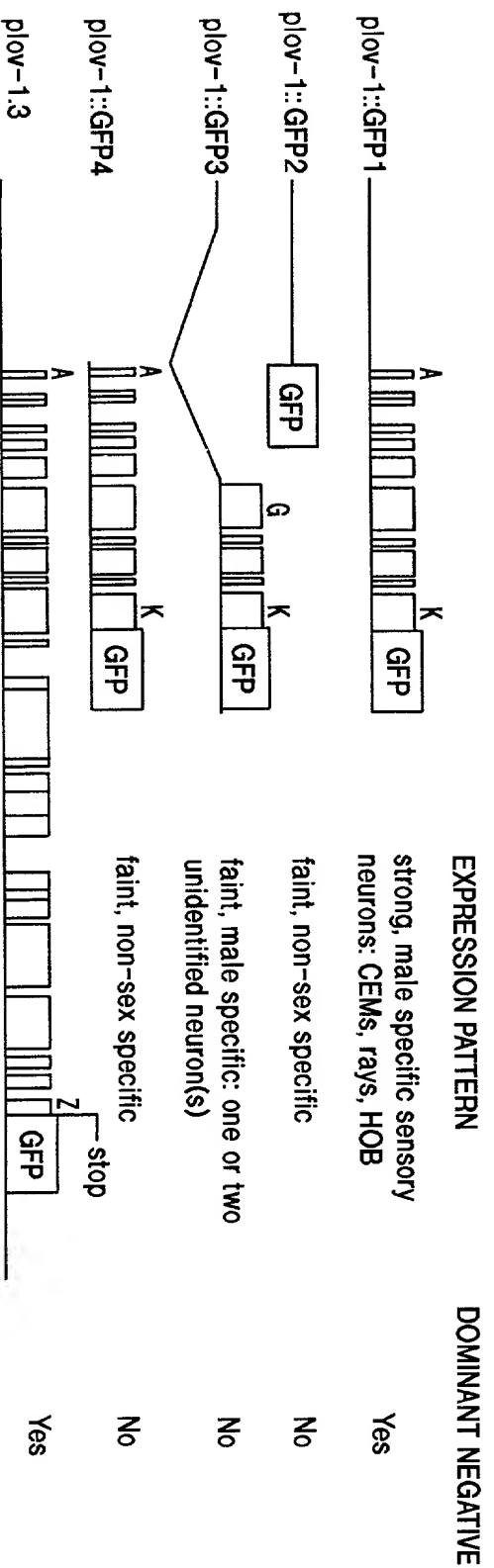


FIG. 2C

• •

	Gly rich			
Ser/Thr-rich		*	1	2

20% (558)

2

21% (586)

2

26% (352)

2

coiled-coil

Variable	Mean	SD	Min	Max
Age	38.5	10.2	25	55
Gender	0.5	0.5	0	1
Marital Status	0.6	0.5	0	1
Education	12.5	1.5	10	15
Income	3500	1500	1000	7000
Health	0.8	0.2	0	1
Stress	4.5	1.5	1	7
Depression	0.3	0.4	0	1
Life Satisfaction	5.5	1.5	1	9
Work Satisfaction	6.5	1.5	1	9
Family Satisfaction	7.5	1.5	1	9
Community Satisfaction	6.0	1.5	1	9
Overall Satisfaction	6.5	1.5	1	9

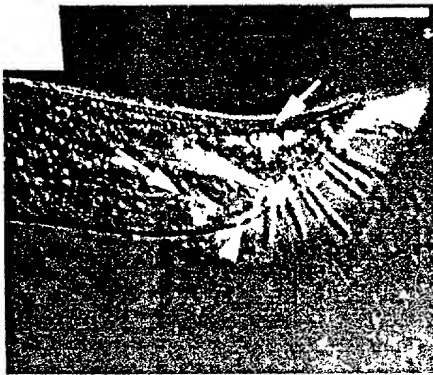


FIG. 4A

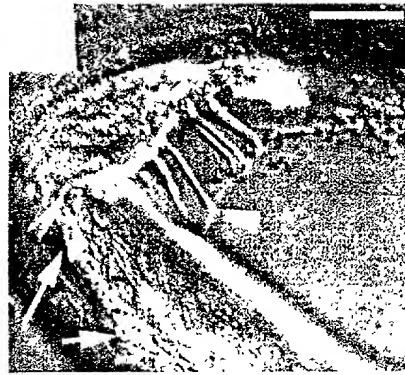


FIG. 4D



FIG. 4B



FIG. 4E



FIG. 4C

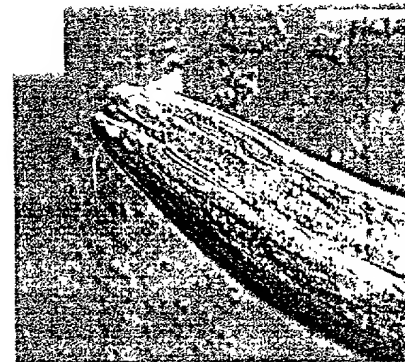


FIG. 4F

005060-0915960

DECLARATION FOR PATENT APPLICATION

As below-named inventors, we hereby declare that:

Our residences, post office addresses, and citizenships are as stated below next to our names.

We believe we are the original, first, and joint inventors of the subject matter which is claimed and for which a patent is sought on the invention entitled:

**POLYCYSTIC KIDNEY DISEASE GENE HOMOLOGS REQUIRED FOR
MALE MATING BEHAVIOR IN NEMATODES AND ASSAYS BASED THEREON**

the specification of which

- () is attached hereto.
 (X) was filed by an authorized person on my behalf on January 6, 2000 as Application Serial No. 09/479,467.
 () and amended by a Preliminary Amendment filed _____.

We hereby state that we have reviewed and understand the contents of the above-identified specification, including the claims as amended by any amendment referred to above.

We acknowledge the duty to disclose information which is material to the examination of this application in accordance with Title 37, Code of Federal Regulations, §1.56(a).

We hereby claim foreign priority benefits under Title 35, United States Code, §119(a)-(d) or §365(b) of any foreign application(s) for patent or inventor's certificate listed below and so identified, or §365(a) of any PCT international application that designated at least one country other than the United States of America, listed below, and we have also identified below any foreign application for patent or inventor's certificate or PCT international application on this invention filed by us or our legal representatives or assigns and having a filing date before that of the application on which priority is claimed.

<u>Number</u>	<u>Country</u>	<u>Day/Month/Year Filed</u>	<u>Priority Claimed (Yes or No)</u>
N/A			

We hereby claim benefit under Title 35, United States Code, §119(e) of any United States provisional application(s) listed below:

<u>Application Serial No.</u>	<u>Filing Date</u>
60/115,127	

We hereby claim the benefit under Title 35, United States Code, §120 of any United States application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by the first paragraph of Title 35, United States Code, §112, we acknowledge the duty to disclose material information as defined in Title 37, Code of Federal Regulations, §1.56(a) which occurred between the filing date of the prior application and the national or PCT international filing date of this application:

<u>Application Serial No.</u>	<u>Filing Date</u>	<u>Status</u>
N/A		

<u>PCT Application No.</u>	<u>Filing Date</u>	<u>Status</u>
N/A		

We hereby declare that all statements made herein of our own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

We hereby appoint the following attorneys and agents, with full power of substitution and revocation, to prosecute this application and to transact all business in the United States Patent and Trademark Office connected therewith and request that all correspondence and telephone calls in respect to this application be directed to Stephanie Seidman, HELLER EHRMAN WHITE & McAULIFFE, 4250 Executive Square, 7th Floor, La Jolla, California 92037-9103:

<u>Attorney</u>	<u>Reg. No.</u>
Stephanie Seidman	33,779
Gary Silverstein	39,372
Peng Chen	43,543
Paula K. Schoeneck	39,362
Dale L. Rieger	43,045

Address for correspondence:

Stephanie Seidman
HELLER EHRMAN WHITE & McAULIFFE
4250 Executive Square
7th Floor
La Jolla, CA 92037-9103

Full name of joint inventor:

Paul W. Sternberg

Inventor's signature:

Paul W. Sternberg

Date:

Feb. 2, 2000

Residence:

Pasadena, California

Post Office Address:

1782 Rose Villa Street, Pasadena, California 91106

Citizenship:

U.S.A.

Full name of joint inventor:

Maureen M. Barr

Inventor's signature:

Maureen M Barr

Date:

2/8/00

Residence:

Pasadena, California

Post Office Address:

2412 Seneca St., Pasadena, California 91107

Citizenship:

U.S.A.

SEQUENCE LISTING

<110> Sternberg, Paul W.
Barr, Maureen M.

<120> POLYCYSTIC KIDNEY DISEASE GENE HOMOLOGS REQUIRED FOR MALE MATING
BEHAVIOR IN NEMATODES AND ASSAYS BASED THEREON

<130> 18021-2901B

<140> Unassigned
<141> 2000-09-05

<150> 09/479,467
<151> 2000-01-06

<150> 60/115,127
<151> 1999-01-06

<160> 16

<170> PatentIn Ver. 2.0

<210> 1
<211> 12912
<212> DNA
<213> Homo sapiens PKD-1 gene

<220>
<221> CDS
<222> (1)..(12912)

<400> 1
atg ccg ccc gcc gcg ccc gcc cgc ctg gcg ctg gcc ctg ggc ctg ggc 48
Met Pro Pro Ala Ala Pro Ala Arg Leu Ala Leu Ala Leu Gly Leu Gly
1 5 10 15
ctg tgg ctc ggg gcg ctg gcg ggg ggg ccc ggg cgc ggc tgc ggg ccc 96
Leu Trp Leu Gly Ala Leu Ala Gly Gly Pro Gly Arg Gly Cys Gly Pro
20 25 30
tgc gag ccc ccc tgc ctc tgc ggg cca gcg ccc ggc gcc gcc tgc cgc 144
Cys Glu Pro Pro Cys Leu Cys Gly Pro Ala Pro Gly Ala Ala Cys Arg
35 40 45
gtc aac tgc tcg ggc cgc ggg ctg cgg acg ctc ggt ccc gcg ctg cgc 192
Val Asn Cys Ser Gly Arg Gly Leu Arg Thr Leu Gly Pro Ala Leu Arg
50 55 60
atc ccc gcg gac gcc aca gag cta gac gtc tcc cac aac ctg ctc cgg 240
Ile Pro Ala Asp Ala Thr Glu Leu Asp Val Ser His Asn Leu Leu Arg
65 70 75 80
gcg ctg gac gtt ggg ctc ctg gcg aac ctc tcg gcg ctg gca gag ctg 288
Ala Leu Asp Val Gly Leu Leu Ala Asn Leu Ser Ala Leu Ala Glu Leu
85 90 95
gat ata agc aac aac aag att tct acg tta gaa gaa gga ata ttt gct 336
Asp Ile Ser Asn Asn Lys Ile Ser Thr Leu Glu Glu Gly Ile Phe Ala
100 105 110
aat tta ttt aat tta agt gaa ata aac ctg agt ggg aac ccg ttt gag 384
Asn Leu Phe Asn Leu Ser Glu Ile Asn Leu Ser Gly Asn Pro Phe Glu
115 120 125
tgt gac tgt ggc ctg gcg tgg ctg ccg caa tgg gcg gag gag cag cag 432
Cys Asp Cys Gly Leu Ala Trp Leu Pro Gln Trp Ala Glu Glu Gln Gln

Ala	Val	His	Pro	Leu	Cys	Pro	Ser	Asp	Thr	Glu	Ile	Phe	Pro	Gly	Asn	
				405					410					415		
ggg	cac	tgc	tac	cgc	ctg	gtg	gtg	gag	aag	gcg	gcc	tgg	ctg	cag	gcg	1296
Gly	His	Cys	Tyr	Arg	Leu	Val	Val	Glu	Lys	Ala	Ala	Trp	Leu	Gln	Ala	
			420					425					430			
cag	gag	cag	tgt	cag	gcc	tgg	gcc	ggg	gcc	gcc	ctg	gca	atg	gtg	gac	1344
Gln	Glu	Gln	Cys	Gln	Ala	Trp	Ala	Gly	Ala	Ala	Leu	Ala	Met	Val	Asp	
		435					440					445				
agt	ccc	gcc	gtg	cag	cgc	ttc	ctg	gtc	tcc	cgg	gtc	acc	agg	agc	cta	1392
Ser	Pro	Ala	Val	Gln	Arg	Phe	Leu	Val	Ser	Arg	Val	Thr	Arg	Ser	Leu	
	450					455					460					
gac	gtg	tgg	atc	ggc	ttc	tgc	act	gtg	cag	ggg	gtg	gag	gtg	ggc	cca	1440
Asp	Val	Trp	Ile	Gly	Phe	Ser	Thr	Val	Gln	Gly	Val	Glu	Val	Gly	Pro	
	465			470						475					480	
gcg	ccg	cag	ggc	gag	gcc	ttc	agc	ctg	gag	agc	tgc	cag	aac	tgg	ctg	1488
Ala	Pro	Gln	Gly	Glu	Ala	Phe	Ser	Leu	Glu	Ser	Cys	Gln	Asn	Trp	Leu	
				485					490					495		
ccc	ggg	gag	cca	cac	cca	gcc	aca	gcc	gag	cac	tgc	gtc	cgg	ctc	ggg	1536
Pro	Gly	Glu	Pro	His	Pro	Ala	Thr	Ala	Glu	His	Cys	Val	Arg	Leu	Gly	
			500					505					510			
ccc	acc	ggg	tgg	tgt	aac	acc	gac	ctg	tgc	tca	gcg	ccg	cac	agc	tac	1584
Pro	Thr	Gly	Trp	Cys	Asn	Thr	Asp	Leu	Cys	Ser	Ala	Pro	His	Ser	Tyr	
		515					520					525				
gtc	tgc	gag	ctg	cag	ccc	gga	ggc	cca	gtg	cag	gat	gcc	gag	aac	ctc	1632
Val	Cys	Glu	Leu	Gln	Pro	Gly	Gly	Pro	Val	Gln	Asp	Ala	Glu	Asn	Leu	
	530					535					540					
ctc	gtg	gga	gcg	ccc	agt	ggg	gac	ctg	cag	gga	ccc	ctg	acg	cct	ctg	1680
Leu	Val	Gly	Ala	Pro	Ser	Gly	Asp	Leu	Gln	Gly	Pro	Leu	Thr	Pro	Leu	
	545				550					555					560	
gca	cag	cag	gac	ggc	ctc	tca	gcc	ccg	cac	gag	ccc	gtg	gag	gtc	atg	1728
Ala	Gln	Gln	Asp	Gly	Leu	Ser	Ala	Pro	His	Glu	Pro	Val	Glu	Val	Met	
			565				570							575		
gta	ttc	ccg	ggc	ctg	cgt	ctg	agc	cgt	gaa	gcc	ttc	ctc	acc	acg	gcc	1776
Val	Phe	Pro	Gly	Leu	Arg	Leu	Ser	Arg	Glu	Ala	Phe	Leu	Thr	Thr	Ala	
			580					585					590			
gaa	ttt	ggg	acc	cag	gag	ctc	cgg	cgg	ccc	gcc	cag	ctg	cgg	ctg	cag	1824
Glu	Phe	Gly	Thr	Gln	Glu	Leu	Arg	Arg	Pro	Ala	Gln	Leu	Arg	Leu	Gln	
		595					600					605				
gtg	tac	cgg	ctc	ctc	agc	aca	gca	ggg	acc	ccg	gag	aac	ggc	agc	gag	1872
Val	Tyr	Arg	Leu	Leu	Ser	Thr	Ala	Gly	Thr	Pro	Glu	Asn	Gly	Ser	Glu	
	610					615					620					
cct	gag	agc	agg	tcc	ccg	gac	aac	agg	acc	cag	ctg	gcc	ccc	gcg	tgc	1920
Pro	Glu	Ser	Arg	Ser	Pro	Asp	Asn	Arg	Thr	Gln	Leu	Ala	Pro	Ala	Cys	
	625				630					635					640	
atg	cca	ggg	gga	cgc	tgg	tgc	cct	gga	gcc	aac	atc	tgc	ttg	ccg	ctg	1968
Met	Pro	Gly	Gly	Arg	Trp	Cys	Pro	Gly	Ala	Asn	Ile	Cys	Leu	Pro	Leu	
				645				650						655		
gac	gcc	tcc	tgc	cac	ccc	cag	gcc	tgc	gcc	aat	ggc	tgc	acg	tca	ggg	2016
Asp	Ala	Ser	Cys	His	Pro	Gln	Ala	Cys	Ala	Asn	Gly	Cys	Thr	Ser	Gly	
			660					665					670			

gta ctg cag gga gtc cta gtg agg tac agc ccc gtg gtg gag gcc ggc	2880
Val Leu Gln Gly Val Leu Val Arg Tyr Ser Pro Val Val Glu Ala Gly	
945 950 955 960	
tcg gac atg gtc ttc cgg tgg acc atc aac gac aag cag tcc ctg acc	2928
Ser Asp Met Val Phe Arg Trp Thr Ile Asn Asp Lys Gln Ser Leu Thr	
965 970 975	
ttc cag aac gtg gtc ttc aat gtc att tat cag agc gcg gcg gtc ttc	2976
Phe Gln Asn Val Val Phe Asn Val Ile Tyr Gln Ser Ala Ala Val Phe	
980 985 990	
aag ctc tca ctg acg gcc tcc aac cac gtg agc aac gtc acc gtg aac	3024
Lys Leu Ser Leu Thr Ala Ser Asn His Val Ser Asn Val Thr Val Asn	
995 1000 1005	
tac aac gta acc gtg gag cgg atg aac agg atg cag ggt ctg cag gtc	3072
Tyr Asn Val Thr Val Glu Met Asn Arg Met Gln Gly Leu Gln Val	
1010 1015 1020	
tcc aca gtg ccg gcc gtg ctg tcc ccc aat gcc acg cta gca ctg acg	3120
Ser Thr Val Pro Ala Val Leu Ser Pro Asn Ala Thr Leu Ala Leu Thr	
1025 1030 1035 1040	
gcg ggc gtg ctg gtg gac tcg gcc gtg gag gtg gcc ttc ctg tgg acc	3168
Ala Gly Val Leu Val Asp Ser Ala Val Glu Val Ala Phe Leu Trp Thr	
1045 1050 1055	
ttt ggg gat ggg gag cag gcc ctc cac cag ttc cag cct ccg tac aac	3216
Phe Gly Asp Gly Glu Gln Ala Leu His Gln Phe Gln Pro Pro Tyr Asn	
1060 1065 1070	
gag tcc ttc cca gtt cca gac ccc tcg gtg gcc cag gtg ctg gtg gag	3264
Glu Ser Phe Pro Val Pro Asp Pro Ser Val Ala Gln Val Leu Val Glu	
1075 1080 1085	
cac aat gtc acg cac acc tac gct gcc cca ggt gag tac ctc ctg acc	3312
His Asn Val Thr His Thr Tyr Ala Ala Pro Gly Glu Tyr Leu Leu Thr	
1090 1095 1100	
gtg ctg gca tct aat gcc ttc gag aac ctg acg cag cag gtg cct gtg	3360
Val Leu Ala Ser Asn Ala Phe Glu Asn Leu Thr Gln Gln Val Pro Val	
1105 1110 1115 1120	
agc gtg cgc gcc tcc ctg ccc tcc gtg gct gtg ggt gtg agt gac ggc	3408
Ser Val Arg Ala Ser Leu Pro Ser Val Ala Val Gly Val Ser Asp Gly	
1125 1130 1135	
gtc ctg gtg gcc ggc cgg ccc gtc acc ttc tac ccg cac ccg ctg ccc	3456
Val Leu Val Ala Gly Arg Pro Val Thr Phe Tyr Pro His Pro Leu Pro	
1140 1145 1150	
tcg cct ggg ggt gtt ctt tac acg tgg gac ttc ggg gac ggc tcc cct	3504
Ser Pro Gly Gly Val Leu Tyr Thr Trp Asp Phe Gly Asp Gly Ser Pro	
1155 1160 1165	
gtc ctg acc cag agc cag ccg gct gcc aac cac acc tat gcc tcg agg	3552
Val Leu Thr Gln Ser Gln Pro Ala Ala Asn His Thr Tyr Ala Ser Arg	
1170 1175 1180	
ggc acc tac cac gtg cgc ctg gag gtc aac aac acg gtg agc ggt gcg	3600
Gly Thr Tyr His Val Arg Leu Glu Val Asn Asn Thr Val Ser Gly Ala	
1185 1190 1195 1200	
gcg gcc cag gcg gat gtg cgc gtc ttt gag gag ctc cgc gga ctc agc	3648
Ala Ala Gln Ala Asp Val Arg Val Phe Glu Glu Leu Arg Gly Leu Ser	

1205	1210	1215	
gtg gac atg agc ctg gcc gtg gag cag gcc gcc ccc gtg gtg gtc agc Val Asp Met Ser Leu Ala Val Glu Gln Gly Ala Pro Val Val Val Ser 1220 1225 1230			3696
gcc gcg gtg cag acg gcc gac aac atc acg tgg acc ttc gac atg ggg Ala Ala Val Gln Thr Gly Asp Asn Ile Thr Trp Thr Phe Asp Met Gly 1235 1240 1245			3744
gac gcc acc gtg ctg tgc gcc ccg gag gca aca gtg gag cat gtg tac Asp Gly Thr Val Leu Ser Gly Pro Glu Ala Thr Val Glu His Val Tyr 1250 1255 1260			3792
ctg cgg gca cag aac tgc aca gtg acc gtg ggt gcg gcc agc ccc gcc Leu Arg Ala Gln Asn Cys Thr Val Thr Val Gly Ala Gly Ser Pro Ala 1265 1270 1275 1280			3840
ggc cac ctg gcc cgg agc ctg cac gtg ctg gtc ttc gtc ctg gag gtg Gly His Leu Ala Arg Ser Leu His Val Leu Val Phe Val Leu Glu Val 1285 1290 1295			3888
ctg cgc gtt gaa ccc gcc gcc tgc atc ccc acg cag cct gac gcg cgg Leu Arg Val Glu Pro Ala Ala Cys Ile Pro Thr Gln Pro Asp Ala Arg 1300 1305 1310			3936
ctc acg gcc tac gtc acc ggg aac ccg gcc cac tac ctc ttc gac tgg Leu Thr Ala Tyr Val Thr Gly Asn Pro Ala His Tyr Leu Phe Asp Trp 1315 1320 1325			3984
acc ttc ggg gat gcc tcc tcc aac acg acc gtg cgg ggg tgc ccg acg Thr Phe Gly Asp Gly Ser Ser Asn Thr Thr Val Arg Gly Cys Pro Thr 1330 1335 1340			4032
gtg aca cac aac ttc acg cgg agc gcc acg ttc ccc ctg gcg ctg gtg Val Thr His Asn Phe Thr Arg Ser Gly Thr Phe Pro Leu Ala Leu Val 1345 1350 1355 1360			4080
ctg tcc agc cgc gtg aac agg gcg cat tac ttc acc agc atc tgc gtg Leu Ser Ser Arg Val Asn Arg Ala His Tyr Phe Thr Ser Ile Cys Val 1365 1370 1375			4128
gag cca gag gtg gcc aac gtc acc ctg cag cca gag agg cag ttt gtg Glu Pro Glu Val Gly Asn Val Thr Leu Gln Pro Glu Arg Gln Phe Val 1380 1385 1390			4176
cag ctc ggg gac gag gcc tgg ctg gtg gca tgt gcc tgg ccc ccg ttc Gln Leu Gly Asp Glu Ala Trp Leu Val Ala Cys Ala Trp Pro Pro Phe 1395 1400 1405			4224
ccc tac cgc tac acc tgg gac ttt gcc acc gag gaa gcc gcc ccc acc Pro Tyr Arg Tyr Thr Trp Asp Phe Gly Thr Glu Glu Ala Ala Pro Thr 1410 1415 1420			4272
cgt gcc agg gcc cct gag gtg acg ttc atc tac cga gac cca gcc tcc Arg Ala Arg Gly Pro Glu Val Thr Phe Ile Tyr Arg Asp Pro Gly Ser 1425 1430 1435 1440			4320
tat ctt gtg aca gtc acc gcg tcc aac aac atc tct gct gcc aat gac Tyr Leu Val Thr Val Thr Ala Ser Asn Asn Ile Ser Ala Ala Asn Asp 1445 1450 1455			4368
tca gcc ctg gtg gag gtg cag gag ccc gtg ctg gtc acc agc atc aag Ser Ala Leu Val Glu Val Gln Glu Pro Val Leu Val Thr Ser Ile Lys 1460 1465 1470			4416
gtc aat gcc tcc ctt ggg ctg gag ctg cag cag ccg tac ctg ttc tct			4464

Val	Asn	Gly	Ser	Leu	Gly	Leu	Glu	Leu	Gln	Gln	Pro	Tyr	Leu	Phe	Ser		
	1475						1480					1485					
gct	gtg	ggc	cgt	ggg	cgc	ccc	gcc	agc	tac	ctg	tgg	gat	ctg	ggg	gac	4512	
Ala	Val	Gly	Arg	Gly	Arg	Pro	Ala	Ser	Tyr	Leu	Trp	Asp	Leu	Gly	Asp		
	1490					1495				1500							
ggt	ggg	tgg	ctc	gag	ggt	ccg	gag	gtc	acc	cac	gct	tac	aac	agc	aca	4560	
Gly	Gly	Trp	Leu	Glu	Gly	Pro	Glu	Val	Thr	His	Ala	Tyr	Asn	Ser	Thr		
	1505				1510					1515					1520		
ggt	gac	ttc	acc	gtt	agg	gtg	gcc	ggc	tgg	aat	gag	gtg	agc	cgc	agc	4608	
Gly	Asp	Phe	Thr	Val	Arg	Val	Ala	Gly	Trp	Asn	Glu	Val	Ser	Arg	Ser		
			1525						1530					1535			
gag	gcc	tgg	ctc	aat	gtg	acg	gtg	aag	cgg	cgc	gtg	cgg	ggg	ctc	gtc	4656	
Glu	Ala	Trp	Leu	Asn	Val	Thr	Val	Lys	Arg	Arg	Val	Arg	Gly	Leu	Val		
			1540					1545					1550				
gtc	aat	gca	agc	cgc	acg	gtg	gtg	ccc	ctg	aat	ggg	agc	gtg	agc	ttc	4704	
Val	Asn	Ala	Ser	Arg	Thr	Val	Val	Pro	Leu	Asn	Gly	Ser	Val	Ser	Phe		
	1555					1560					1565						
agc	acg	tcg	ctg	gag	gcc	ggc	agt	gat	gtg	cgc	tat	tcc	tgg	gtg	ctc	4752	
Ser	Thr	Ser	Leu	Glu	Ala	Gly	Ser	Asp	Val	Arg	Tyr	Ser	Trp	Val	Leu		
	1570					1575					1580						
tgt	gac	cgc	tgc	acg	ccc	atc	cct	ggg	ggt	cct	acc	atc	tct	tac	acc	4800	
Cys	Asp	Arg	Cys	Thr	Pro	Ile	Pro	Gly	Gly	Pro	Thr	Ile	Ser	Tyr	Thr		
	1585				1590					1595					1600		
ttc	cgc	tcc	gtg	ggc	acc	ttc	aat	atc	atc	gtc	acg	gct	gag	aac	gag	4848	
Phe	Arg	Ser	Val	Gly	Thr	Phe	Asn	Ile	Ile	Val	Thr	Ala	Glu	Asn	Glu		
			1605					1610						1615			
gtg	ggc	tcc	gcc	cag	gac	agc	atc	ttc	gtc	tat	gtc	ctg	cag	ctc	ata	4896	
Val	Gly	Ser	Ala	Gln	Asp	Ser	Ile	Phe	Val	Tyr	Val	Leu	Gln	Leu	Ile		
			1620				1625						1630				
gag	ggg	ctg	cag	gtg	gtg	ggc	ggt	ggc	cgc	tac	ttc	ccc	acc	aac	cac	4944	
Glu	Gly	Leu	Gln	Val	Val	Gly	Gly	Gly	Arg	Tyr	Phe	Pro	Thr	Asn	His		
	1635					1640					1645						
acg	gta	cag	ctg	cag	gcc	gtg	gtt	agg	gat	ggc	acc	aac	gtc	tcc	tac	4992	
Thr	Val	Gln	Leu	Gln	Ala	Val	Val	Arg	Asp	Gly	Thr	Asn	Val	Ser	Tyr		
	1650					1655					1660						
agc	tgg	act	gcc	tgg	agg	gac	agg	ggc	ccg	gcc	ctg	gcc	ggc	agc	ggc	5040	
Ser	Trp	Thr	Ala	Trp	Arg	Asp	Arg	Gly	Pro	Ala	Leu	Ala	Gly	Ser	Gly		
	1665				1670				1675						1680		
aaa	ggc	ttc	tcg	ctc	acc	gtg	ctc	gag	gcc	ggc	acc	tac	cat	gtg	cag	5088	
Lys	Gly	Phe	Ser	Leu	Thr	Val	Leu	Glu	Ala	Gly	Thr	Tyr	His	Val	Gln		
			1685						1690					1695			
ctg	cgg	gcc	acc	aac	atg	ctg	ggc	agc	gcc	tgg	gcc	gac	tgc	acc	atg	5136	
Leu	Arg	Ala	Thr	Asn	Met	Leu	Gly	Ser	Ala	Trp	Ala	Asp	Cys	Thr	Met		
			1700					1705					1710				
gac	ttc	gtg	gag	cct	gtg	ggg	tgg	ctg	atg	gtg	gcc	gcc	tcc	ccg	aac	5184	
Asp	Phe	Val	Glu	Pro	Val	Gly	Trp	Leu	Met	Val	Ala	Ala	Ser	Pro	Asn		
	1715					1720						1725					
cca	gct	gcc	gtc	aac	aca	agc	gtc	acc	ctc	agt	gcc	gag	ctg	gct	ggt	5232	
Pro	Ala	Ala	Val	Asn	Thr	Ser	Val	Thr	Leu	Ser	Ala	Glu	Leu	Ala	Gly		
	1730					1735					1740						

ggc agt ggt gtc gta tac act tgg tcc ttg gag gag ggg ctg agc tgg	5280
Gly Ser Gly Val Val Tyr Thr Trp Ser Leu Glu Glu Gly Leu Ser Trp	
1745 1750 1755 1760	
gag acc tcc gag cca ttt acc acc cat agc ttc ccc aca ccc ggc ctg	5328
Glu Thr Ser Glu Pro Phe Thr Thr His Ser Phe Pro Thr Pro Gly Leu	
1765 1770 1775	
cac ttg gtc acc atg acg gca ggg aac ccg ctg ggc tca gcc aac gcc	5376
His Leu Val Thr Met Thr Ala Gly Asn Pro Leu Gly Ser Ala Asn Ala	
1780 1785 1790	
acc gtg gaa gtg gat gtg cag gtg cct gtg agt ggc ctg agc atc agg	5424
Thr Val Glu Val Asp Val Gln Val Pro Val Ser Gly Leu Ser Ile Arg	
1795 1800 1805	
gcc agc gag ccc gga ggc agc ttc gtg gcg gcc ggg tcc tct gtg ccc	5472
Ala Ser Glu Pro Gly Gly Ser Phe Val Ala Ala Gly Ser Ser Val Pro	
1810 1815 1820	
ttt tgg ggg cag ctg gcc acg ggc acc aat gtg agc tgg tgc tgg gct	5520
Phe Trp Gly Gln Leu Ala Thr Gly Thr Asn Val Ser Trp Cys Trp Ala	
1825 1830 1835 1840	
gtg ccc ggc ggc agc agc aag cgt ggc cct cat gtc acc atg gtc ttc	5568
Val Pro Gly Gly Ser Ser Lys Arg Gly Pro His Val Thr Met Val Phe	
1845 1850 1855	
ccg gat gct ggc acc ttc tcc atc cgg ctg aat gcc tcc aac gca gtc	5616
Pro Asp Ala Gly Thr Phe Ser Ile Arg Leu Asn Ala Ser Asn Ala Val	
1860 1865 1870	
agc tgg gtc tca gcc acg tac aac ctg acg gcg gag gag ccc atc gtg	5664
Ser Trp Val Ser Ala Thr Tyr Asn Leu Thr Ala Glu Glu Pro Ile Val	
1875 1880 1885	
ggc ctg gtg ctg tgg gcc agc agc aag gtg gtg gcg ccc ggg cag ctg	5712
Gly Leu Val Leu Trp Ala Ser Ser Lys Val Val Ala Pro Gly Gln Leu	
1890 1895 1900	
gtc cat ttt cag atc ctg ctg gct gcc ggc tca gct gtc acc ttc cgc	5760
Val His Phe Gln Ile Leu Ala Ala Gly Ser Ala Val Thr Phe Arg	
1905 1910 1915 1920	
cta cag gtc ggc ggg gcc aac ccc gag gtg ctg ccc ggg ccc cgt ttc	5808
Leu Gln Val Gly Gly Ala Asn Pro Glu Val Leu Pro Gly Pro Arg Phe	
1925 1930 1935	
tcc cac agc ttc ccc cgc gtc gga gac cac gtg gtg agc gtg cgg ggc	5856
Ser His Ser Phe Pro Arg Val Gly Asp His Val Val Ser Val Arg Gly	
1940 1945 1950	
aaa aac cac gtg agc tgg gcc cag gcg cag gtg cgc atc gtg gtg ctg	5904
Lys Asn His Val Ser Trp Ala Gln Ala Gln Val Arg Ile Val Val Leu	
1955 1960 1965	
gag gcc gtg agt ggg ctg cag gtg ccc aac tgc tgc gag cct ggc atc	5952
Glu Ala Val Ser Gly Leu Gln Val Pro Asn Cys Cys Glu Pro Gly Ile	
1970 1975 1980	
gcc acg ggc act gag agg aac ttc aca gcc cgc gtg cag cgc ggc tct	6000
Ala Thr Gly Thr Glu Arg Asn Phe Thr Ala Arg Val Gln Arg Gly Ser	
1985 1990 1995 2000	
cgg gtc gcc tac gcc tgg tac ttc tcg ctg cag aag gtc cag ggc gac	6048
Arg Val Ala Tyr Ala Trp Tyr Phe Ser Leu Gln Lys Val Gln Gly Asp	
2005 2010 2015	

tcg ctg gtc atc ctg tcg ggc cgc gac gtc acc tac acg ccc gtg gcc Ser Leu Val Ile Leu Ser Gly Arg Asp Val Thr Tyr Thr Pro Val Ala 2020 2025 2030	6096
gcg ggg ctg ttg gag atc cag gtg cgc gcc ttc aac gcc ctg ggc agt Ala Gly Leu Leu Glu Ile Gln Val Arg Ala Phe Asn Ala Leu Gly Ser 2035 2040 2045	6144
gag aac cgc acg ctg gtg ctg gag gtt cag gac gcc gtc cag tat gtg Glu Asn Arg Thr Leu Val Leu Glu Val Gln Asp Ala Val Gln Tyr Val 2050 2055 2060	6192
gcc ctg cag agc ggc ccc tgc ttc acc aac cgc tcg gcg cag ttt gag Ala Leu Gln Ser Gly Pro Cys Phe Thr Asn Arg Ser Ala Gln Phe Glu 2065 2070 2075 2080	6240
gcc gcc acc agc ccc agc ccc cgg cgt gtg gcc tac cac tgg gac ttt Ala Ala Thr Ser Pro Ser Pro Arg Arg Val Ala Tyr His Trp Asp Phe 2085 2090 2095	6288
ggg gat ggg tcg cca ggg cag gac aca gat gag ccc agg gcc gag cac Gly Asp Gly Ser Pro Gly Gln Asp Thr Asp Glu Pro Arg Ala Glu His 2100 2105 2110	6336
tcc tac ctg agg cct ggg gac tac cgc gtg cag gtg aac gcc tcc aac Ser Tyr Leu Arg Pro Gly Asp Tyr Arg Val Gln Val Asn Ala Ser Asn 2115 2120 2125	6384
ctg gtg agc ttc ttc gtg gcg cag gcc acg gtg acc gtc cag gtg ctg Leu Val Ser Phe Phe Val Ala Gln Ala Thr Val Thr Val Gln Val Leu 2130 2135 2140	6432
gcc tgc cgg gag ccg gag gtg gac gtg gtc ctg ccc ctg cag gtg ctg Ala Cys Arg Glu Pro Glu Val Asp Val Val Leu Pro Leu Gln Val Leu 2145 2150 2155 2160	6480
atg cgg cga tca cag cgc aac tac ttg gag gcc cac gtt gac ctg cgc Met Arg Arg Ser Gln Arg Asn Tyr Leu Glu Ala His Val Asp Leu Arg 2165 2170 2175	6528
gac tgc gtc acc tac cag act gag tac cgc tgg gag gtg tat cgc acc Asp Cys Val Thr Tyr Gln Thr Glu Tyr Arg Trp Glu Val Tyr Arg Thr 2180 2185 2190	6576
gcc agc tgc cag cgg ccg ggg cgc cca gcg cgt gtg gcc ctg ccc ggc Ala Ser Cys Gln Arg Pro Gly Arg Pro Ala Arg Val Ala Leu Pro Gly 2195 2200 2205	6624
gtg gac gtg agc cgg cct cgg ctg gtg ctg ccg cgg ctg gcg ctg cct Val Asp Val Ser Arg Pro Arg Leu Val Leu Pro Arg Leu Ala Leu Pro 2210 2215 2220	6672
gtg ggg cac tac tgc ttt gtg ttt gtc gtg tca ttt ggg gac acg cca Val Gly His Tyr Cys Phe Val Phe Val Val Ser Phe Gly Asp Thr Pro 2225 2230 2235 2240	6720
ctg aca cag agc atc cag gcc aat gtg acg gtg gcc ccc gag cgc ctg Leu Thr Gln Ser Ile Gln Ala Asn Val Thr Val Ala Pro Glu Arg Leu 2245 2250 2255	6768
gtg ccc atc att gag ggt ggc tca tac cgc gtg tgg tca gac aca cgg Val Pro Ile Ile Glu Gly Gly Ser Tyr Arg Val Trp Ser Asp Thr Arg 2260 2265 2270	6816
gac ctg gtg ctg gat ggg agc gag tcc tac gac ccc aac ctg gag gac Asp Leu Val Leu Asp Gly Ser Glu Ser Tyr Asp Pro Asn Leu Glu Asp 2280 2285 2290	6864

2275	2280	2285	
ggc gac cag acg ccg ctc agt ttc cac tgg gcc tgt gtg gct tcg aca			6912
Gly Asp Gln Thr Pro Leu Ser Phe His Trp Ala Cys Val Ala Ser Thr			
2290	2295	2300	
cag agg gag gct ggc ggg tgt gcg ctg aac ttt ggg ccc cgc ggg agc			6960
Gln Arg Glu Ala Gly Gly Cys Ala Leu Asn Phe Gly Pro Arg Gly Ser			
2305	2310	2315	2320
agc acg gtc acc att cca cgg gag cgg ctg gcg gct ggc gtg gag tac			7008
Ser Thr Val Thr Ile Pro Arg Glu Arg Leu Ala Ala Gly Val Glu Tyr			
2325	2330	2335	
acc ttc agc ctg acc gtg tgg aag gcc ggc cgc aag gag gag gcc acc			7056
Thr Phe Ser Leu Thr Val Trp Lys Ala Gly Arg Lys Glu Glu Ala Thr			
2340	2345	2350	
aac cag acg gtg ctg atc cgg agt ggc cgg gtg ccc att gtg tcc ttg			7104
Asn Gln Thr Val Leu Ile Arg Ser Gly Arg Val Pro Ile Val Ser Leu			
2355	2360	2365	
gag tgt gtg tcc tgc aag gca cag gcc gtg tac gaa gtg agc cgc agc			7152
Glu Cys Val Ser Cys Lys Ala Gln Ala Val Tyr Glu Val Ser Arg Ser			
2370	2375	2380	
tcc tac gtg tac ttg gag ggc cgc tgc ctc aat tgc agc agc ggc tcc			7200
Ser Tyr Val Tyr Leu Glu Gly Arg Cys Leu Asn Cys Ser Ser Gly Ser			
2385	2390	2395	2400
aag cga ggg cgg tgg gct gca cgt acg ttc agc aac aag acg ctg gtg			7248
Lys Arg Gly Arg Trp Ala Ala Arg Thr Phe Ser Asn Lys Thr Leu Val			
2405	2410	2415	
ctg gat gag acc acc aca tcc acg ggc agt gca ggc atg cga ctg gtg			7296
Leu Asp Glu Thr Thr Thr Ser Thr Gly Ser Ala Gly Met Arg Leu Val			
2420	2425	2430	
ctg cgg cgg ggc gtg ctg cgg gac ggc gag gga tac acc ttc acg ctc			7344
Leu Arg Arg Gly Val Leu Arg Asp Gly Glu Gly Tyr Thr Phe Thr Leu			
2435	2440	2445	
acg gtg ctg ggc cgc tct ggc gag gag gag ggc tgc gcc tcc atc cgc			7392
Thr Val Leu Gly Arg Ser Gly Glu Glu Glu Gly Cys Ala Ser Ile Arg			
2450	2455	2460	
ctg tcc ccc aac cgc ccg ccg ctg ggg ggc tct tgc cgc ctc ttc cca			7440
Leu Ser Pro Asn Arg Pro Pro Leu Gly Gly Ser Cys Arg Leu Phe Pro			
2465	2470	2475	2480
ctg ggc gct gtg cac gcc ctc acc acc aag gtg cac ttc gaa tgc acg			7488
Leu Gly Ala Val His Ala Leu Thr Thr Lys Val His Phe Glu Cys Thr			
2485	2490	2495	
ggc tgg cat gac gcg gag gat gct ggc gcc ccg ctg gtg tac gcc ctg			7536
Gly Trp His Asp Ala Glu Asp Ala Gly Ala Pro Leu Val Tyr Ala Leu			
2500	2505	2510	
ctg ctg cgg cgc tgt cgc cag ggc cac tgc gag gag ttc tgt gtc tac			7584
Leu Leu Arg Arg Cys Arg Gln Gly His Cys Glu Glu Phe Cys Val Tyr			
2515	2520	2525	
aag ggc agc ctc tcc agc tac gga gcc gtg ctg ccc ccg ggt ttc agg			7632
Lys Gly Ser Leu Ser Ser Tyr Gly Ala Val Leu Pro Pro Gly Phe Arg			
2530	2535	2540	
cca cac ttc gag gtg ggc ctg gcc gtg gtg gtg cag gac cag ctg gga			7680

Pro His Phe Glu Val Gly Leu Ala Val Val Val Gln Asp Gln Leu Gly	
2545 2550 2555 2560	
gcc gct gtg gtc gcc ctc aac agg tct ttg gcc atc acc ctc cca gag	7728
Ala Ala Val Val Ala Leu Asn Arg Ser Leu Ala Ile Thr Leu Pro Glu	
2565 2570 2575	
ccc aac ggc agc gca acg ggg ctc aca gtc tgg ctg cac ggg ctc acc	7776
Pro Asn Gly Ser Ala Thr Gly Leu Thr Val Trp Leu His Gly Leu Thr	
2580 2585 2590	
gct agt gtg ctc cca ggg ctg ctg cgg cag gcc gat ccc cag cac gtc	7824
Ala Ser Val Leu Pro Gly Leu Leu Arg Gln Ala Asp Pro Gln His Val	
2595 2600 2605	
atc gag tac tcg ttg gcc ctg gtc acc gtg ctg aac gag tac gag cgg	7872
Ile Glu Tyr Ser Leu Ala Leu Val Thr Val Leu Asn Glu Tyr Glu Arg	
2610 2615 2620	
gcc ctg gac gtg gcg gca gag ccc aag cac gag cgg cag cac cga gcc	7920
Ala Leu Asp Val Ala Ala Glu Pro Lys His Glu Arg Gln His Arg Ala	
2625 2630 2635 2640	
cag ata cgc aag aac atc acg gag act ctg gtg tcc ctg agg gtc cac	7968
Gln Ile Arg Lys Asn Ile Thr Glu Thr Leu Val Ser Leu Arg Val His	
2645 2650 2655	
act gtg gat gac atc cag cag atc gct gct gcg ctg gcc cag tgc atg	8016
Thr Val Asp Asp Ile Gln Gln Ile Ala Ala Ala Leu Ala Gln Cys Met	
2660 2665 2670	
ggg ccc agc agg gag ctc gta tgc cgc tcg tgc ctg aag cag acg ctg	8064
Gly Pro Ser Arg Glu Leu Val Cys Arg Ser Cys Leu Lys Gln Thr Leu	
2675 2680 2685	
cac aag ctg gag gcc atg atg ctc atc ctg cag gca gag acc acc gcg	8112
His Lys Leu Glu Ala Met Met Leu Ile Leu Gln Ala Glu Thr Thr Ala	
2690 2695 2700	
ggc acc gtg acg ccc acc gcc atc gga gac agc atc ctc aac atc aca	8160
Gly Thr Val Thr Pro Thr Ala Ile Gly Asp Ser Ile Leu Asn Ile Thr	
2705 2710 2715 2720	
gga gac ctc atc cac ctg gcc agc tcg gac gtg cgg gca cca cag ccc	8208
Gly Asp Leu Ile His Leu Ala Ser Ser Asp Val Arg Ala Pro Gln Pro	
2725 2730 2735	
tca gag ctg gga gcc gag tca cca tct cgg atg gtg gcg tcc cag gcc	8256
Ser Glu Leu Gly Ala Glu Ser Pro Ser Arg Met Val Ala Ser Gln Ala	
2740 2745 2750	
tac aac ctg acc tct gcc ctc atg cgc atc ctc atg cgc tcc cgc gtg	8304
Tyr Asn Leu Thr Ser Ala Leu Met Arg Ile Leu Met Arg Ser Arg Val	
2755 2760 2765	
ctc aac gag gag ccc ctg acg ctg gcg ggc gag gag atc gtg gcc cag	8352
Leu Asn Glu Glu Pro Leu Thr Leu Ala Gly Glu Glu Ile Val Ala Gln	
2770 2775 2780	
ggc aag cgc tcg gac ccg cgg agc ctg ctg tgc tat ggc ggc gcc cca	8400
Gly Lys Arg Ser Asp Pro Arg Ser Leu Leu Cys Tyr Gly Gly Ala Pro	
2785 2790 2795 2800	
ggg cct ggc tgc cac ttc tcc atc ccc gag gct ttc agc ggg gcc ctg	8448
Gly Pro Gly Cys His Phe Ser Ile Pro Glu Ala Phe Ser Gly Ala Leu	
2805 2810 2815	

gcc aac ctc agt gac gtg gtg cag ctc atc ttt ctg gtg gac tcc aat	8496
Ala Asn Leu Ser Asp Val Val Gln Leu Ile Phe Leu Val Asp Ser Asn	
2820 2825 2830	
ccc ttt ccc ttt ggc tat atc agc aac tac acc gtc tcc acc aag gtg	8544
Pro Phe Pro Phe Gly Tyr Ile Ser Asn Tyr Thr Val Ser Thr Lys Val	
2835 2840 2845	
gcc tcg atg gca ttc cag aca cag gcc ggc gcc cag atc ccc atc gag	8592
Ala Ser Met Ala Phe Gln Thr Gln Ala Gly Ala Gln Ile Pro Ile Glu	
2850 2855 2860	
cgg ctg gcc tca gag cgc gcc atc acc gtg aag gtg ccc aac aac tcg	8640
Arg Leu Ala Ser Glu Arg Ala Ile Thr Val Lys Val Pro Asn Asn Ser	
2865 2870 2875 2880	
gac tgg gct gcc cgg ggc cac cgc agc tcc gcc aac tcc gcc aac tcc	8688
Asp Trp Ala Ala Arg Gly His Arg Ser Ser Ala Asn Ser Ala Asn Ser	
2885 2890 2895	
gtt gtg gtc cag ccc cag gcc tcc gtc ggt gct gtg gtc acc ctg gac	8736
Val Val Val Gln Pro Gln Ala Ser Val Gly Ala Val Val Thr Leu Asp	
2900 2905 2910	
agc agc aac cct gcg gcc ggg ctg cat ctg cag ctc aac tat acg ctg	8784
Ser Ser Asn Pro Ala Ala Gly Leu His Leu Gln Leu Asn Tyr Thr Leu	
2915 2920 2925	
ctg gac ggc cac tac ctg tct gag gaa cct gag ccc tac ctg gca gtc	8832
Leu Asp Gly His Tyr Leu Ser Glu Glu Pro Glu Pro Tyr Leu Ala Val	
2930 2935 2940	
tac cta cac tcg gag ccc cgg ccc aat gag cac aac tgc tcg gct agc	8880
Tyr Leu His Ser Glu Pro Arg Pro Asn Glu His Asn Cys Ser Ala Ser	
2945 2950 2955 2960	
agg agg atc cgc cca gag tca ctc cag ggt gct gac cac cgg ccc tac	8928
Arg Arg Ile Arg Pro Glu Ser Leu Gln Gly Ala Asp His Arg Pro Tyr	
2965 2970 2975	
acc ttc ttc att tcc ccg ggg agc aga gac cca gcg ggg agt tac cat	8976
Thr Phe Phe Ile Ser Pro Gly Ser Arg Asp Pro Ala Gly Ser Tyr His	
2980 2985 2990	
ctg aac ctc tcc agc cac ttc cgc tgg tcg gcg ctg cag gtg tcc gtg	9024
Leu Asn Leu Ser Ser His Phe Arg Trp Ser Ala Leu Gln Val Ser Val	
2995 3000 3005	
ggc ctg tac acg tcc ctg tgc cag tac ttc agc gag gag gac atg gtg	9072
Gly Leu Tyr Thr Ser Leu Cys Gln Tyr Phe Ser Glu Glu Asp Met Val	
3010 3015 3020	
tgg cgg aca gag ggg ctg ctg ccc ctg gag gag acc tcg ccc cgc cag	9120
Trp Arg Thr Glu Gly Leu Leu Pro Leu Glu Glu Thr Ser Pro Arg Gln	
3025 3030 3035 3040	
gcc gtc tgc ctc acc cgc cac ctc acc gcc ttc ggc gcc agc ctc ttc	9168
Ala Val Cys Leu Thr Arg His Leu Thr Ala Phe Gly Ala Ser Leu Phe	
3045 3050 3055	
gtg ccc cca agc cat gtc cgc ttt gtg ttt cct gag ccg aca gcg gat	9216
Val Pro Pro Ser His Val Arg Phe Val Phe Pro Glu Pro Thr Ala Asp	
3060 3065 3070	
gta aac tac atc gtc atg ctg aca tgt gct gtg tgc ctg gtg acc tac	9264
Val Asn Tyr Ile Val Met Leu Thr Cys Ala Val Cys Leu Val Thr Tyr	
3075 3080 3085	

atg gtc atg gcc gcc atc ctg cac aag ctg gac cag ttg gat gcc agc	9312
Met Val Met Ala Ala Ile Leu His Lys Leu Asp Gln Leu Asp Ala Ser	
3090 3095 3100	
cgg ggc cgc gcc atc cct ttc tgt ggg cag cgg ggc cgc ttc aag tac	9360
Arg Gly Arg Ala Ile Pro Phe Cys Gly Gln Arg Gly Arg Phe Lys Tyr	
3105 3110 3115 3120	
gag atc ctc gtc aag aca ggc tgg ggc cgg ggc tca ggt acc acg gcc	9408
Glu Ile Leu Val Lys Thr Gly Trp Gly Arg Gly Ser Gly Thr Thr Ala	
3125 3130 3135	
cac gtg ggc atc atg ctg tat ggg gtg gac agc cgg agc ggc cac cgg	9456
His Val Gly Ile Met Leu Tyr Gly Val Asp Ser Arg Ser Gly His Arg	
3140 3145 3150	
cac ctg gac ggc gac aga gcc ttc cac cgc aac agc ctg gac atc ttc	9504
His Leu Asp Gly Asp Arg Ala Phe His Arg Asn Ser Leu Asp Ile Phe	
3155 3160 3165	
cgg atc gcc acc ccg cac agc ctg ggt agc gtg tgg aag atc cga gtg	9552
Arg Ile Ala Thr Pro His Ser Leu Gly Ser Val Trp Lys Ile Arg Val	
3170 3175 3180	
tgg cac gac aac aaa ggg ctc agc cct gcc tgg ttc ctg cag cac gtc	9600
Trp His Asp Asn Lys Gly Leu Ser Pro Ala Trp Phe Leu Gln His Val	
3185 3190 3195 3200	
atc gtc agg gac ctg cag acg gca cgc agc gcc ttc ttc ctg gtc aat	9648
Ile Val Arg Asp Leu Gln Thr Ala Arg Ser Ala Phe Phe Leu Val Asn	
3205 3210 3215	
gac tgg ctt tcg gtg gag acg gag gcc aac ggg ggc ctg gtg gag aag	9696
Asp Trp Leu Ser Val Glu Thr Glu Ala Asn Gly Gly Leu Val Glu Lys	
3220 3225 3230	
gag gtg ctg gcc gcg agc gac gca gcc ctt ttg cgc ttc cgg cgc ctg	9744
Glu Val Leu Ala Ala Ser Asp Ala Ala Leu Leu Arg Phe Arg Arg Leu	
3235 3240 3245	
ctg gtg gct gag ctg cag cgt ggc ttc ttt gac aag cac atc tgg ctc	9792
Leu Val Ala Glu Leu Gln Arg Gly Phe Phe Asp Lys His Ile Trp Leu	
3250 3255 3260	
tcc ata tgg gac cgg ccg cct cgt agc cgt ttc act cgc atc cag agg	9840
Ser Ile Trp Asp Arg Pro Pro Arg Ser Arg Phe Thr Arg Ile Gln Arg	
3265 3270 3275 3280	
gcc acc tgc tgc gtt ctc ctc atc tgc ctc ttc ctg ggc gcc aac gcc	9888
Ala Thr Cys Cys Val Leu Leu Ile Cys Leu Phe Leu Gly Ala Asn Ala	
3285 3290 3295	
gtg tgg tac ggg gct gtt ggc gac tct gcc tac agc acg ggg cat gtg	9936
Val Trp Tyr Gly Ala Val Gly Asp Ser Ala Tyr Ser Thr Gly His Val	
3300 3305 3310	
tcc agg ctg agc ccg ctg agc gtc gac aca gtc gct gtt ggc ctg gtg	9984
Ser Arg Leu Ser Pro Leu Ser Val Asp Thr Val Ala Val Gly Leu Val	
3315 3320 3325	
tcc agc gtg gtt gtc tat ccc gtc tac ctg gcc atc ctt ttt ctc ttc	10032
Ser Ser Val Val Val Tyr Pro Val Tyr Leu Ala Ile Leu Phe Leu Phe	
3330 3335 3340	
cgg atg tcc cgg agc aag gtg gct ggg agc ccg agc ccc aca cct gcc	10080
Arg Met Ser Arg Ser Lys Val Ala Gly Ser Pro Ser Pro Thr Pro Ala	

3345	3350	3355	3360	
ggg cag cag gtg ctg gac atc gac agc tgc ctg gac tcg tcc gtg ctg				10128
Gly Gln Gln Val Leu Asp Ile Asp Ser Cys Leu Asp Ser Ser Val Leu	3365	3370	3375	
gac agc tcc ttc ctc acg ttc tca ggc ctc cac gct gag cag gcc ttt				10176
Asp Ser Ser Phe Leu Thr Phe Ser Gly Leu His Ala Glu Gln Ala Phe	3380	3385	3390	
gtt gga cag atg aag agt gac ttg ttt ctg gat gat tct aag agt ctg				10224
Val Gly Gln Met Lys Ser Asp Leu Phe Leu Asp Asp Ser Lys Ser Leu	3395	3400	3405	
gtg tgc tgg ccc tcc ggc gag gga acg ctc agt tgg ccg gac ctg ctc				10272
Val Cys Trp Pro Ser Gly Glu Gly Thr Leu Ser Trp Pro Asp Leu Leu	3410	3415	3420	
agt gac ccg tcc att gtg ggt agc aat ctg cgg cag ctg gca cgg ggc				10320
Ser Asp Pro Ser Ile Val Gly Ser Asn Leu Arg Gln Leu Ala Arg Gly	3425	3430	3435	3440
cag gcg ggc cat ggg ctg ggc cca gag gag gac ggc ttc tcc ctg gcc				10368
Gln Ala Gly His Gly Leu Gly Pro Glu Glu Asp Gly Phe Ser Leu Ala	3445	3450	3455	
agc ccc tac tcg cct gcc aaa tcc ttc tca gca tca gat gaa gac ctg				10416
Ser Pro Tyr Ser Pro Ala Lys Ser Phe Ser Ala Ser Asp Glu Asp Leu	3460	3465	3470	
atc cag cag gtc ctt gcc gag ggg gtc agc agc cca gcc cct acc caa				10464
Ile Gln Gln Val Leu Ala Glu Gly Val Ser Ser Pro Ala Pro Thr Gln	3475	3480	3485	
gac acc cac atg gaa acg gac ctg ctc agc agc ctg tcc agc act cct				10512
Asp Thr His Met Glu Thr Asp Leu Leu Ser Ser Leu Ser Ser Thr Pro	3490	3495	3500	
ggg gag aag aca gag acg ctg gcg ctg cag agg ctg ggg gag ctg ggg				10560
Gly Glu Lys Thr Glu Thr Leu Ala Leu Gln Arg Leu Gly Glu Leu Gly	3505	3510	3515	3520
cca ccc agc cca ggc ctg aac tgg gaa cag ccc cag gca gcg agg ctg				10608
Pro Pro Ser Pro Gly Leu Asn Trp Glu Gln Pro Gln Ala Ala Arg Leu	3525	3530	3535	
tcc agg aca gga ctg gtg gag ggt ctg cgg aag cgc ctg ctg ccg gcc				10656
Ser Arg Thr Gly Leu Val Glu Gly Leu Arg Lys Arg Leu Leu Pro Ala	3540	3545	3550	
tgg tgt gcc tcc ctg gcc cac ggg ctc agc ctg ctc ctg gtg gct gtg				10704
Trp Cys Ala Ser Leu Ala His Gly Leu Ser Leu Leu Leu Val Ala Val	3555	3560	3565	
gct gtg gct gtc tca ggg tgg gtg ggt gcg agc ttc ccc ccg ggc gtg				10752
Ala Val Ala Val Ser Gly Trp Val Gly Ala Ser Phe Pro Pro Gly Val	3570	3575	3580	
agt gtt gcg tgg ctc ctg tcc agc agc gcc agc ttc ctg gcc tca ttc				10800
Ser Val Ala Trp Leu Leu Ser Ser Ser Ala Ser Phe Leu Ala Ser Phe	3585	3590	3595	3600
ctc ggc tgg gag cca ctg aag gtc ttg ctg gaa gcc ctg tac ttc tca				10848
Leu Gly Trp Glu Pro Leu Lys Val Leu Leu Glu Ala Leu Tyr Phe Ser	3605	3610	3615	
ctg gtg gcc aag cgg ctg cac ccg gat gaa gat gac acc ctg gta gag				10896

Leu	Val	Ala	Lys	Arg	Leu	His	Pro	Asp	Glu	Asp	Asp	Thr	Leu	Val	Glu	
3620			3625			3630										
agc	ccg	gct	gtg	acg	cct	gtg	agc	gca	cgt	gtg	ccc	cgc	gta	cgg	cca	10944
Ser	Pro	Ala	Val	Thr	Pro	Val	Ser	Ala	Arg	Val	Pro	Arg	Val	Arg	Pro	
3635			3640			3645										
ccc	cac	ggc	ttt	gca	ctc	ttc	ctg	gcc	aag	gaa	gaa	gcc	cgc	aag	gtc	10992
Pro	His	Gly	Phe	Ala	Leu	Phe	Leu	Ala	Lys	Glu	Glu	Ala	Arg	Lys	Val	
3650			3655			3660										
aag	agg	cta	cat	ggc	atg	ctg	cgg	agc	ctc	ctg	gtg	tac	atg	ctt	ttt	11040
Lys	Arg	Leu	His	Gly	Met	Leu	Arg	Ser	Leu	Leu	Val	Tyr	Met	Leu	Phe	
3665			3670			3675			3680							
ctg	ctg	gtg	acc	ctg	ctg	gcc	agc	tat	ggg	gat	gcc	tca	tgc	cat	ggg	11088
Leu	Leu	Val	Thr	Leu	Leu	Ala	Ser	Tyr	Gly	Asp	Ala	Ser	Cys	His	Gly	
3685			3690			3695										
cac	gcc	tac	cgt	ctg	caa	agc	gcc	atc	aag	cag	gag	ctg	cac	agc	cgg	11136
His	Ala	Tyr	Arg	Leu	Gln	Ser	Ala	Ile	Lys	Gln	Glu	Leu	His	Ser	Arg	
3700			3705			3710										
gcc	ttc	ctg	gcc	atc	acg	cgg	tct	gag	gag	ctc	tgg	cca	tgg	atg	gcc	11184
Ala	Phe	Leu	Ala	Ile	Thr	Arg	Ser	Glu	Glu	Leu	Trp	Pro	Trp	Met	Ala	
3715			3720			3725										
cac	gtg	ctg	ctg	ccc	tac	gtc	cac	ggg	aac	cag	tcc	agc	cca	gag	ctg	11232
His	Val	Leu	Leu	Pro	Tyr	Val	His	Gly	Asn	Gln	Ser	Ser	Pro	Glu	Leu	
3730			3735			3740										
ggg	ccc	cca	cgg	ctg	cgg	cag	gtg	cgg	ctg	cag	gaa	gca	ctc	tac	cca	11280
Gly	Pro	Pro	Arg	Leu	Arg	Gln	Val	Arg	Leu	Gln	Glu	Ala	Leu	Tyr	Pro	
3745			3750			3755			3760							
gac	cct	ccc	ggc	ccc	agg	gtc	cac	acg	tgc	tcg	gcc	gca	gga	ggc	ttc	11328
Asp	Pro	Pro	Gly	Pro	Arg	Val	His	Thr	Cys	Ser	Ala	Ala	Gly	Gly	Phe	
3765			3770			3775										
agc	acc	agc	gat	tac	gac	gtt	ggc	tgg	gag	agt	cct	cac	aat	ggc	tcg	11376
Ser	Thr	Ser	Asp	Tyr	Asp	Val	Gly	Trp	Glu	Ser	Pro	His	Asn	Gly	Ser	
3780			3785			3790										
ggg	acg	tgg	gcc	tat	tca	gcg	ccg	gat	ctg	ctg	ggg	gca	tgg	tcc	tgg	11424
Gly	Thr	Trp	Ala	Tyr	Ser	Ala	Pro	Asp	Leu	Leu	Gly	Ala	Trp	Ser	Trp	
3795			3800			3805										
ggc	tcc	tgt	gcc	gtg	tat	gac	agc	ggg	ggc	tac	gtg	cag	gag	ctg	ggc	11472
Gly	Ser	Cys	Ala	Val	Tyr	Asp	Ser	Gly	Gly	Tyr	Val	Gln	Glu	Leu	Gly	
3810			3815			3820										
ctg	agc	ctg	gag	gag	agc	cgc	gac	cgg	ctg	cgc	ttc	ctg	cag	ctg	cac	11520
Leu	Ser	Leu	Glu	Glu	Ser	Arg	Asp	Arg	Leu	Arg	Phe	Leu	Gln	Leu	His	
3825			3830			3835			3840							
aac	tgg	ctg	gac	aac	agg	agc	cgc	gct	gtg	ttc	ctg	gag	ctc	acg	cgc	11568
Asn	Trp	Leu	Asp	Asn	Arg	Ser	Arg	Ala	Val	Phe	Leu	Glu	Leu	Thr	Arg	
3845			3850			3855										
tac	agc	ccg	gcc	gtg	ggg	ctg	cac	gcc	gcc	gtc						

gcg	ctg	cgc	cgc	ctc	agc	gcg	ggc	ctc	tgc	ctg	cct	ctg	ctc	acc	tgc	11712
Ala	Leu	Arg	Arg	Leu	Ser	Ala	Gly	Leu	Ser	Leu	Pro	Leu	Leu	Thr	Ser	
3890						3895				3900						
gtg	tgc	ctg	ctg	ctg	ttc	gcc	gtg	cac	ttc	gcc	gtg	gcc	gag	gcc	cgt	11760
Val	Cys	Leu	Leu	Leu	Phe	Ala	Val	His	Phe	Ala	Val	Ala	Glu	Ala	Arg	
3905				3910				3915				3920				
act	tgg	cac	agg	gaa	ggg	cgc	tgg	cgc	gtg	ctg	cgg	ctc	gga	gcc	tgg	11808
Thr	Trp	His	Arg	Glu	Gly	Arg	Trp	Arg	Val	Leu	Arg	Leu	Gly	Ala	Trp	
				3925				3930				3935				
gcg	cgg	tgg	ctg	ctg	gtg	gcg	ctg	acg	gcg	gcc	acg	gca	ctg	gta	cgc	11856
Ala	Arg	Trp	Leu	Leu	Val	Ala	Leu	Thr	Ala	Ala	Thr	Ala	Leu	Val	Arg	
		3940				3945				3950						
ctc	gcc	cag	ctg	ggt	gcc	gct	gac	cgc	cag	tgg	acc	cgt	ttc	gtg	cgc	11904
Leu	Ala	Gln	Leu	Gly	Ala	Ala	Asp	Arg	Gln	Trp	Thr	Arg	Phe	Val	Arg	
3955				3960				3965								
ggc	cgc	cgc	cgc	cgc	ttc	act	agc	ttc	gac	cag	gtg	gcg	cac	gtg	agc	11952
Gly	Arg	Pro	Arg	Arg	Phe	Thr	Ser	Phe	Asp	Gln	Val	Ala	His	Val	Ser	
3970				3975				3980								
tcc	gca	gcc	cgt	ggc	ctg	gcg	gcc	tgc	ctg	ctc	ttc	ctg	ctt	ttg	gtc	12000
Ser	Ala	Ala	Arg	Gly	Leu	Ala	Ala	Ser	Leu	Leu	Phe	Leu	Leu	Leu	Val	
3985				3990				3995				4000				
aag	gct	gcc	cag	cac	gta	cgc	ttc	gtg	cgc	cag	tgg	tcc	gtc	ttt	ggc	12048
Lys	Ala	Ala	Gln	His	Val	Arg	Phe	Val	Arg	Gln	Trp	Ser	Val	Phe	Gly	
		4005				4010				4015						
aag	aca	tta	tgc	cga	gct	ctg	cca	gag	ctc	ctg	ggg	gtc	acc	ttg	ggc	12096
Lys	Thr	Leu	Cys	Arg	Ala	Leu	Pro	Glu	Leu	Leu	Gly	Val	Thr	Leu	Gly	
		4020				4025				4030						
ctg	gtg	gtg	ctc	ggg	gta	gcc	tac	gcc	cag	ctg	gcc	atc	ctg	ctc	gtg	12144
Leu	Val	Val	Leu	Gly	Val	Ala	Tyr	Ala	Gln	Leu	Ala	Ile	Leu	Leu	Val	
4035				4040				4045								
tct	tcc	tgt	gtg	gac	tcc	ctc	tgg	agc	gtg	gcc	cag	gcc	ctg	ttg	gtg	12192
Ser	Ser	Cys	Val	Asp	Ser	Leu	Trp	Ser	Val	Ala	Gln	Ala	Leu	Leu	Val	
4050				4055				4060								
ctg	tgc	cct	ggg	act	ggg	ctc	tct	acc	ctg	tgt	cct	gcc	gag	tcc	tgg	12240
Leu	Cys	Pro	Gly	Thr	Gly	Leu	Ser	Thr	Leu	Cys	Pro	Ala	Glu	Ser	Trp	
4065				4070				4075				4080				
cac	ctg	tca	ccc	ctg	ctg	tgt	gtg	ggg	ctc	tgg	gca	ctg	cgg	ctg	tgg	12288
His	Leu	Ser	Pro	Leu	Leu	Cys	Val	Gly	Leu	Trp	Ala	Leu	Arg	Leu	Trp	
		4085				4090				4095						
ggc	gcc	cta	cgg	ctg	ggg	gct	gtt	att	ctc	cgc						

ctg ccc tct cgc tcc tcc agg ggc tcc aag gta tcc ccg gat gtg ccc	12528
Leu Pro Ser Arg Ser Ser Arg Gly Ser Lys Val Ser Pro Asp Val Pro	
4165 4170 4175	
cca ccc agc gct ggc tcc gat gcc tcg cac ccc tcc acc tcc tcc agc	12576
Pro Pro Ser Ala Gly Ser Asp Ala Ser His Pro Ser Thr Ser Ser Ser	
4180 4185 4190	
cag ctg gat ggg ctg agc gtg agc ctg ggc cgg ctg ggg aca agg tgt	12624
Gln Leu Asp Gly Leu Ser Val Ser Leu Gly Arg Leu Gly Thr Arg Cys	
4195 4200 4205	
gag cct gag ccc tcc cgc ctc caa gcc gtg ttc gag gcc ctg ctc acc	12672
Glu Pro Glu Pro Ser Arg Leu Gln Ala Val Phe Glu Ala Leu Leu Thr	
4210 4215 4220	
cag ttt gac cga ctc aac cag gcc aca gag gac gtc tac cag ctg gag	12720
Gln Phe Asp Arg Leu Asn Gln Ala Thr Glu Asp Val Tyr Gln Leu Glu	
4225 4230 4235 4240	
cag cag ctg cac agc ctg caa ggc cgc agg agc agc cgg gcg ccc gcc	12768
Gln Gln Leu His Ser Leu Gln Gly Arg Arg Ser Ser Arg Ala Pro Ala	
4245 4250 4255	
gga tct tcc cgt ggc cca tcc ccg ggc ctg cgg cca gca ctg ccc agc	12816
Gly Ser Ser Arg Gly Pro Ser Pro Gly Leu Arg Pro Ala Leu Pro Ser	
4260 4265 4270	
cgc ctt gcc cgg gcc agt cgg ggt gtg gac ctg gcc act ggc ccc agc	12864
Arg Leu Ala Arg Ala Ser Arg Gly Val Asp Leu Ala Thr Gly Pro Ser	
4275 4280 4285	
agg aca ccc ctt cgg gcc aag aac aag gtc cac ccc agc agc act tag	12912
Arg Thr Pro Leu Arg Ala Lys Asn Lys Val His Pro Ser Ser Thr	
4290 4295 4300	

<210> 2
 <211> 4303
 <212> PRT
 <213> Homo sapiens PKD-1 protein

<400> 2
 Met Pro Pro Ala Ala Pro Ala Arg Leu Ala Leu Ala Leu Gly Leu Gly
 1 5 10 15
 Leu Trp Leu Gly Ala Leu Ala Gly Gly Pro Gly Arg Gly Cys Gly Pro
 20 25 30
 Cys Glu Pro Pro Cys Leu Cys Gly Pro Ala Pro Gly Ala Ala Cys Arg
 35 40 45
 Val Asn Cys Ser Gly Arg Gly Leu Arg Thr Leu Gly Pro Ala Leu Arg
 50 55 60
 Ile Pro Ala Asp Ala Thr Glu Leu Asp Val Ser His Asn Leu Leu Arg
 65 70 75 80
 Ala Leu Asp Val Gly Leu Leu Ala Asn Leu Ser Ala Leu Ala Glu Leu
 85 90 95
 Asp Ile Ser Asn Asn Lys Ile Ser Thr Leu Glu Glu Gly Ile Phe Ala
 100 105 110
 Asn Leu Phe Asn Leu Ser Glu Ile Asn Leu Ser Gly Asn Pro Phe Glu
 115 120 125

Cys Asp Cys Gly Leu Ala Trp Leu Pro Gln Trp Ala Glu Glu Gln Gln
 130 135 140
 Val Arg Val Val Gln Pro Glu Ala Ala Thr Cys Ala Gly Pro Gly Ser
 145 150 155 160
 Leu Ala Gly Gln Pro Leu Leu Gly Ile Pro Leu Leu Asp Ser Gly Cys
 165 170 175
 Gly Glu Glu Tyr Val Ala Cys Leu Pro Asp Asn Ser Ser Gly Thr Val
 180 185 190
 Ala Ala Val Ser Phe Ser Ala Ala His Glu Gly Leu Leu Gln Pro Glu
 195 200 205
 Ala Cys Ser Ala Phe Cys Phe Ser Thr Gly Gln Gly Leu Ala Ala Leu
 210 215 220
 Ser Glu Gln Gly Trp Cys Leu Cys Gly Ala Ala Gln Pro Ser Ser Ala
 225 230 235 240
 Ser Phe Ala Cys Leu Ser Leu Cys Ser Gly Pro Pro Ala Pro Pro Ala
 245 250 255
 Pro Thr Cys Arg Gly Pro Thr Leu Leu Gln His Val Phe Pro Ala Ser
 260 265 270
 Pro Gly Ala Thr Leu Val Gly Pro His Gly Pro Leu Ala Ser Gly Gln
 275 280 285
 Leu Ala Ala Phe His Ile Ala Ala Pro Leu Pro Val Thr Asp Thr Arg
 290 295 300
 Trp Asp Phe Gly Asp Gly Ser Ala Glu Val Asp Ala Ala Gly Pro Ala
 305 310 315 320
 Ala Ser His Arg Tyr Val Leu Pro Gly Arg Tyr His Val Thr Ala Val
 325 330 335
 Leu Ala Leu Gly Ala Gly Ser Ala Leu Gly Thr Asp Val Gln Val
 340 345 350
 Glu Ala Ala Pro Ala Ala Leu Glu Leu Val Cys Pro Ser Ser Val Gln
 355 360 365
 Ser Asp Glu Ser Leu Asp Leu Ser Ile Gln Asn Arg Gly Gly Ser Gly
 370 375 380
 Leu Glu Ala Ala Tyr Ser Ile Val Ala Leu Gly Glu Glu Pro Ala Arg
 385 390 395 400
 Ala Val His Pro Leu Cys Pro Ser Asp Thr Glu Ile Phe Pro Gly Asn
 405 410 415
 Gly His Cys Tyr Arg Leu Val Val Glu Lys Ala Ala Trp Leu Gln Ala
 420 425 430
 Gln Glu Gln Cys Gln Ala Trp Ala Gly Ala Ala Leu Ala Met Val Asp
 435 440 445
 Ser Pro Ala Val Gln Arg Phe Leu Val Ser Arg Val Thr Arg Ser Leu
 450 455 460
 Asp Val Trp Ile Gly Phe Ser Thr Val Gln Gly Val Glu Val Gly Pro
 465 470 475 480

Ala Pro Gln Gly Glu Ala Phe Ser Leu Glu Ser Cys Gln Asn Trp Leu
 485 490 495
 Pro Gly Glu Pro His Pro Ala Thr Ala Glu His Cys Val Arg Leu Gly
 500 505 510
 Pro Thr Gly Trp Cys Asn Thr Asp Leu Cys Ser Ala Pro His Ser Tyr
 515 520 525
 Val Cys Glu Leu Gln Pro Gly Gly Pro Val Gln Asp Ala Glu Asn Leu
 530 535 540
 Leu Val Gly Ala Pro Ser Gly Asp Leu Gln Gly Pro Leu Thr Pro Leu
 545 550 555 560
 Ala Gln Gln Asp Gly Leu Ser Ala Pro His Glu Pro Val Glu Val Met
 565 570 575
 Val Phe Pro Gly Leu Arg Leu Ser Arg Glu Ala Phe Leu Thr Thr Ala
 580 585 590
 Glu Phe Gly Thr Gln Glu Leu Arg Arg Pro Ala Gln Leu Arg Leu Gln
 595 600 605
 Val Tyr Arg Leu Leu Ser Thr Ala Gly Thr Pro Glu Asn Gly Ser Glu
 610 615 620
 Pro Glu Ser Arg Ser Pro Asp Asn Arg Thr Gln Leu Ala Pro Ala Cys
 625 630 635 640
 Met Pro Gly Gly Arg Trp Cys Pro Gly Ala Asn Ile Cys Leu Pro Leu
 645 650 655
 Asp Ala Ser Cys His Pro Gln Ala Cys Ala Asn Gly Cys Thr Ser Gly
 660 665 670
 Pro Gly Leu Pro Gly Ala Pro Tyr Ala Leu Trp Arg Glu Phe Leu Phe
 675 680 685
 Ser Val Pro Ala Gly Pro Pro Ala Gln Tyr Ser Val Thr Leu His Gly
 690 695 700
 Gln Asp Val Leu Met Leu Pro Gly Asp Leu Val Gly Leu Gln His Asp
 705 710 715 720
 Ala Gly Pro Gly Ala Leu Leu His Cys Ser Pro Ala Pro Gly His Pro
 725 730 735
 Gly Pro Arg Ala Pro Tyr Leu Ser Ala Asn Ala Ser Ser Trp Leu Pro
 740 745 750
 His Leu Pro Ala Gln Leu Glu Gly Thr Trp Gly Cys Pro Ala Cys Ala
 755 760 765
 Leu Arg Leu Leu Ala Gln Arg Glu Gln Leu Thr Val Leu Leu Gly Leu
 770 775 780
 Arg Pro Asn Pro Gly Leu Arg Leu Pro Gly Arg Tyr Glu Val Arg Ala
 785 790 795 800
 Glu Val Gly Asn Gly Val Ser Arg His Asn Leu Ser Cys Ser Phe Asp
 805 810 815
 Val Val Ser Pro Val Ala Gly Leu Arg Val Ile Tyr Pro Ala Pro Arg
 820 825 830
 Asp Gly Arg Leu Tyr Val Pro Thr Asn Gly Ser Ala Leu Val Leu Gln

835					840					845					
Val	Asp	Ser	Gly	Ala	Asn	Ala	Thr	Ala	Thr	Ala	Arg	Trp	Pro	Gly	Gly
850					855					860					
Ser	Leu	Ser	Ala	Arg	Phe	Glu	Asn	Val	Cys	Pro	Ala	Leu	Val	Ala	Thr
865					870					875					880
Phe	Val	Pro	Ala	Cys	Pro	Trp	Glu	Thr	Asn	Asp	Thr	Leu	Phe	Ser	Val
				885					890					895	
Val	Ala	Leu	Pro	Trp	Leu	Ser	Glu	Gly	Glu	His	Val	Val	Asp	Val	Val
			900					905					910		
Val	Glu	Asn	Ser	Ala	Ser	Arg	Ala	Asn	Leu	Ser	Leu	Arg	Val	Thr	Ala
		915					920					925			
Glu	Glu	Pro	Ile	Cys	Gly	Leu	Arg	Ala	Thr	Pro	Ser	Pro	Glu	Ala	Arg
	930					935					940				
Val	Leu	Gln	Gly	Val	Leu	Val	Arg	Tyr	Ser	Pro	Val	Val	Glu	Ala	Gly
945					950					955					960
Ser	Asp	Met	Val	Phe	Arg	Trp	Thr	Ile	Asn	Asp	Lys	Gln	Ser	Leu	Thr
				965					970					975	
Phe	Gln	Asn	Val	Val	Phe	Asn	Val	Ile	Tyr	Gln	Ser	Ala	Ala	Val	Phe
			980					985					990		
Lys	Leu	Ser	Leu	Thr	Ala	Ser	Asn	His	Val	Ser	Asn	Val	Thr	Val	Asn
		995					1000					1005			
Tyr	Asn	Val	Thr	Val	Glu	Arg	Met	Asn	Arg	Met	Gln	Gly	Leu	Gln	Val
	1010					1015					1020				
Ser	Thr	Val	Pro	Ala	Val	Leu	Ser	Pro	Asn	Ala	Thr	Leu	Ala	Leu	Thr
025					1030					1035				1040	
Ala	Gly	Val	Leu	Val	Asp	Ser	Ala	Val	Glu	Val	Ala	Phe	Leu	Trp	Thr
			1045					1050					1055		
Phe	Gly	Asp	Gly	Glu	Gln	Ala	Leu	His	Gln	Phe	Gln	Pro	Pro	Tyr	Asn
		1060					1065					1070			
Glu	Ser	Phe	Pro	Val	Pro	Asp	Pro	Ser	Val	Ala	Gln	Val	Leu	Val	Glu
	1075					1080					1085				
His	Asn	Val	Thr	His	Thr	Tyr	Ala	Ala	Pro	Gly	Glu	Tyr	Leu	Leu	Thr
	1090					1095					1100				
Val	Leu	Ala	Ser	Asn	Ala	Phe	Glu	Asn	Leu	Thr	Gln	Gln	Val	Pro	Val
105					1110					1115				1120	
Ser	Val	Arg	Ala	Ser	Leu	Pro	Ser	Val	Ala	Val	Gly	Val	Ser	Asp	Gly
			1125					1130					1135		
Val	Leu	Val	Ala	Gly	Arg	Pro	Val	Thr	Phe	Tyr	Pro	His	Pro	Leu	Pro
		1140					1145					1150			
Ser	Pro	Gly	Gly	Val	Leu	Tyr	Thr	Trp	Asp	Phe	Gly	Asp	Gly	Ser	Pro
	1155					1160					1165				
Val	Leu	Thr	Gln	Ser	Gln	Pro	Ala	Ala	Asn	His	Thr	Tyr	Ala	Ser	Arg
	1170					1175					1180				
Gly	Thr	Tyr	His	Val	Arg	Leu	Glu	Val	Asn	Asn	Thr	Val	Ser	Gly	Ala
185					1190					1195					1200

Ala	Ala	Gln	Ala	Asp	Val	Arg	Val	Phe	Glu	Glu	Leu	Arg	Gly	Leu	Ser	
				1205					1210					1215		
Val	Asp	Met	Ser	Leu	Ala	Val	Glu	Gln	Gly	Ala	Pro	Val	Val	Val	Ser	
			1220				1225					1230				
Ala	Ala	Val	Gln	Thr	Gly	Asp	Asn	Ile	Thr	Trp	Thr	Phe	Asp	Met	Gly	
		1235				1240					1245					
Asp	Gly	Thr	Val	Leu	Ser	Gly	Pro	Glu	Ala	Thr	Val	Glu	His	Val	Tyr	
	1250				1255						1260					
Leu	Arg	Ala	Gln	Asn	Cys	Thr	Val	Thr	Val	Gly	Ala	Gly	Ser	Pro	Ala	
265				1270						1275					1280	
Gly	His	Leu	Ala	Arg	Ser	Leu	His	Val	Leu	Val	Phe	Val	Leu	Glu	Val	
			1285					1290						1295		
Leu	Arg	Val	Glu	Pro	Ala	Ala	Cys	Ile	Pro	Thr	Gln	Pro	Asp	Ala	Arg	
		1300					1305					1310				
Leu	Thr	Ala	Tyr	Val	Thr	Gly	Asn	Pro	Ala	His	Tyr	Leu	Phe	Asp	Trp	
	1315					1320					1325					
Thr	Phe	Gly	Asp	Gly	Ser	Ser	Asn	Thr	Thr	Val	Arg	Gly	Cys	Pro	Thr	
	1330				1335					1340						
Val	Thr	His	Asn	Phe	Thr	Arg	Ser	Gly	Thr	Phe	Pro	Leu	Ala	Leu	Val	
345			1350						1355						1360	
Leu	Ser	Ser	Arg	Val	Asn	Arg	Ala	His	Tyr	Phe	Thr	Ser	Ile	Cys	Val	
			1365					1370					1375			
Glu	Pro	Glu	Val	Gly	Asn	Val	Thr	Leu	Gln	Pro	Glu	Arg	Gln	Phe	Val	
		1380					1385						1390			
Gln	Leu	Gly	Asp	Glu	Ala	Trp	Leu	Val	Ala	Cys	Ala	Trp	Pro	Pro	Phe	
	1395					1400					1405					
Pro	Tyr	Arg	Tyr	Thr	Trp	Asp	Phe	Gly	Thr	Glu	Glu	Ala	Ala	Pro	Thr	
	1410				1415					1420						
Arg	Ala	Arg	Gly	Pro	Glu	Val	Thr	Phe	Ile	Tyr	Arg	Asp	Pro	Gly	Ser	
425				1430					1435					1440		
Tyr	Leu	Val	Thr	Val	Thr	Ala	Ser	Asn	Asn	Ile	Ser	Ala	Ala	Asn	Asp	
			1445					1450						1455		
Ser	Ala	Leu	Val	Glu	Val	Gln	Glu	Pro	Val	Leu	Val	Thr	Ser	Ile	Lys	
		1460					1465					1470				
Val	Asn	Gly	Ser	Leu	Gly	Leu	Glu	Leu	Gln	Gln	Pro	Tyr	Leu	Phe	Ser	
	1475					1480					1485					
Ala	Val	Gly	Arg	Gly	Arg	Pro	Ala	Ser	Tyr	Leu	Trp	Asp	Leu	Gly	Asp	
	1490				1495					1500						
Gly	Gly	Trp	Leu	Glu	Gly	Pro	Glu	Val	Thr	His	Ala	Tyr	Asn	Ser	Thr	
505				1510					1515					1520		
Gly	Asp	Phe	Thr	Val	Arg	Val	Ala	Gly	Trp	Asn	Glu	Val	Ser	Arg	Ser	
			1525					1530								

Val Asn Ala Ser Arg Thr Val Val Pro Leu Asn Gly Ser Val Ser Phe
 1555 1560 1565
 Ser Thr Ser Leu Glu Ala Gly Ser Asp Val Arg Tyr Ser Trp Val Leu
 1570 1575 1580
 Cys Asp Arg Cys Thr Pro Ile Pro Gly Gly Pro Thr Ile Ser Tyr Thr
 585 1590 1595 1600
 Phe Arg Ser Val Gly Thr Phe Asn Ile Ile Val Thr Ala Glu Asn Glu
 1605 1610 1615
 Val Gly Ser Ala Gln Asp Ser Ile Phe Val Tyr Val Leu Gln Leu Ile
 1620 1625 1630
 Glu Gly Leu Gln Val Val Gly Gly Gly Arg Tyr Phe Pro Thr Asn His
 1635 1640 1645
 Thr Val Gln Leu Gln Ala Val Val Arg Asp Gly Thr Asn Val Ser Tyr
 1650 1655 1660
 Ser Trp Thr Ala Trp Arg Asp Arg Gly Pro Ala Leu Ala Gly Ser Gly
 665 1670 1675 1680
 Lys Gly Phe Ser Leu Thr Val Leu Glu Ala Gly Thr Tyr His Val Gln
 1685 1690 1695
 Leu Arg Ala Thr Asn Met Leu Gly Ser Ala Trp Ala Asp Cys Thr Met
 1700 1705 1710
 Asp Phe Val Glu Pro Val Gly Trp Leu Met Val Ala Ala Ser Pro Asn
 1715 1720 1725
 Pro Ala Ala Val Asn Thr Ser Val Thr Leu Ser Ala Glu Leu Ala Gly
 1730 1735 1740
 Gly Ser Gly Val Val Tyr Thr Trp Ser Leu Glu Glu Gly Leu Ser Trp
 745 1750 1755 1760
 Glu Thr Ser Glu Pro Phe Thr Thr His Ser Phe Pro Thr Pro Gly Leu
 1765 1770 1775
 His Leu Val Thr Met Thr Ala Gly Asn Pro Leu Gly Ser Ala Asn Ala
 1780 1785 1790
 Thr Val Glu Val Asp Val Gln Val Pro Val Ser Gly Leu Ser Ile Arg
 1795 1800 1805
 Ala Ser Glu Pro Gly Gly Ser Phe Val Ala Ala Gly Ser Ser Val Pro
 1810 1815 1820
 Phe Trp Gly Gln Leu Ala Thr Gly Thr Asn Val Ser Trp Cys Trp Ala
 825 1830 1835 1840
 Val Pro Gly Gly Ser Ser Lys Arg Gly Pro His Val Thr Met Val Phe
 1845 1850 1855
 Pro Asp Ala Gly Thr Phe Ser Ile Arg Leu Asn Ala Ser Asn Ala Val
 1860 1865 1870
 Ser Trp Val Ser Ala Thr Tyr Asn Leu Thr Ala Glu Glu Pro Ile Val
 1875 1880 1885
 Gly Leu Val Leu Trp Ala Ser Lys Val Val Ala Pro Gly Gln Leu
 1890 1895 1900
 Val His Phe Gln Ile Leu Leu Ala Ala Gly Ser Ala Val Thr Phe Arg

1905	1910	1915	1920
Leu Gln Val Gly Gly Ala Asn Pro Glu Val Leu Pro Gly Pro Arg Phe	1925	1930	1935
Ser His Ser Phe Pro Arg Val Gly Asp His Val Val Ser Val Arg Gly	1940	1945	1950
Lys Asn His Val Ser Trp Ala Gln Ala Gln Val Arg Ile Val Val Leu	1955	1960	1965
Glu Ala Val Ser Gly Leu Gln Val Pro Asn Cys Cys Glu Pro Gly Ile	1970	1975	1980
Ala Thr Gly Thr Glu Arg Asn Phe Thr Ala Arg Val Gln Arg Gly Ser	1985	1990	1995
Arg Val Ala Tyr Ala Trp Tyr Phe Ser Leu Gln Lys Val Gln Gly Asp	2005	2010	2015
Ser Leu Val Ile Leu Ser Gly Arg Asp Val Thr Tyr Thr Pro Val Ala	2020	2025	2030
Ala Gly Leu Leu Glu Ile Gln Val Arg Ala Phe Asn Ala Leu Gly Ser	2035	2040	2045
Glu Asn Arg Thr Leu Val Leu Glu Val Gln Asp Ala Val Gln Tyr Val	2050	2055	2060
Ala Leu Gln Ser Gly Pro Cys Phe Thr Asn Arg Ser Ala Gln Phe Glu	2065	2070	2075
Ala Ala Thr Ser Pro Ser Pro Arg Arg Val Ala Tyr His Trp Asp Phe	2085	2090	2095
Gly Asp Gly Ser Pro Gly Gln Asp Thr Asp Glu Pro Arg Ala Glu His	2100	2105	2110
Ser Tyr Leu Arg Pro Gly Asp Tyr Arg Val Gln Val Asn Ala Ser Asn	2115	2120	2125
Leu Val Ser Phe Phe Val Ala Gln Ala Thr Val Thr Val Gln Val Leu	2130	2135	2140
Ala Cys Arg Glu Pro Glu Val Asp Val Val Leu Pro Leu Gln Val Leu	2145	2150	2155
Met Arg Arg Ser Gln Arg Asn Tyr Leu Glu Ala His Val Asp Leu Arg	2165	2170	2175
Asp Cys Val Thr Tyr Gln Thr Glu Tyr Arg Trp Glu Val Tyr Arg Thr	2180	2185	2190
Ala Ser Cys Gln Arg Pro Gly Arg Pro Ala Arg Val Ala Leu Pro Gly	2195	2200	2205
Val Asp Val Ser Arg Pro Arg Leu Val Leu Pro Arg Leu Ala Leu Pro	2210	2215	2220
Val Gly His Tyr Cys Phe Val Phe Val Val Ser Phe Gly Asp Thr Pro	2225	2230	2235
Leu Thr Gln Ser Ile Gln Ala Asn Val Thr Val Ala Pro Glu Arg Leu	2245	2250	2255
Val Pro Ile Ile Glu Gly Gly Ser Tyr Arg Val Trp Ser Asp Thr Arg	2260	2265	2270

Ala Leu Asp Val Ala Ala Glu Pro Lys His Glu Arg Gln His Arg Ala
 625 2630 2635 2640
 Gln Ile Arg Lys Asn Ile Thr Glu Thr Leu Val Ser Leu Arg Val His
 2645 2650 2655
 Thr Val Asp Asp Ile Gln Gln Ile Ala Ala Ala Leu Ala Gln Cys Met
 2660 2665 2670
 Gly Pro Ser Arg Glu Leu Val Cys Arg Ser Cys Leu Lys Gln Thr Leu
 2675 2680 2685
 His Lys Leu Glu Ala Met Met Leu Ile Leu Gln Ala Glu Thr Thr Ala
 2690 2695 2700
 Gly Thr Val Thr Pro Thr Ala Ile Gly Asp Ser Ile Leu Asn Ile Thr
 705 2710 2715 2720
 Gly Asp Leu Ile His Leu Ala Ser Ser Asp Val Arg Ala Pro Gln Pro
 2725 2730 2735
 Ser Glu Leu Gly Ala Glu Ser Pro Ser Arg Met Val Ala Ser Gln Ala
 2740 2745 2750
 Tyr Asn Leu Thr Ser Ala Leu Met Arg Ile Leu Met Arg Ser Arg Val
 2755 2760 2765
 Leu Asn Glu Glu Pro Leu Thr Leu Ala Gly Glu Glu Ile Val Ala Gln
 2770 2775 2780
 Gly Lys Arg Ser Asp Pro Arg Ser Leu Leu Cys Tyr Gly Gly Ala Pro
 785 2790 2795 2800
 Gly Pro Gly Cys His Phe Ser Ile Pro Glu Ala Phe Ser Gly Ala Leu
 2805 2810 2815
 Ala Asn Leu Ser Asp Val Val Gln Leu Ile Phe Leu Val Asp Ser Asn
 2820 2825 2830
 Pro Phe Pro Phe Gly Tyr Ile Ser Asn Tyr Thr Val Ser Thr Lys Val
 2835 2840 2845
 Ala Ser Met Ala Phe Gln Thr Gln Ala Gly Ala Gln Ile Pro Ile Glu
 2850 2855 2860
 Arg Leu Ala Ser Glu Arg Ala Ile Thr Val Lys Val Pro Asn Asn Ser
 865 2870 2875 2880
 Asp Trp Ala Ala Arg Gly His Arg Ser Ser Ala Asn Ser Ala Asn Ser
 2885 2890 2895
 Val Val Val Gln Pro Gln Ala Ser Val Gly Ala Val Val Thr Leu Asp
 2900 2905 2910
 Ser Ser Asn Pro Ala Ala Gly Leu His Leu Gln Leu Asn Tyr Thr Leu
 2915 2920 2925
 Leu Asp Gly His Tyr Leu Ser Glu Glu Pro Glu Pro Tyr Leu Ala Val
 2930 2935 2940
 Tyr Leu His Ser Glu Pro Arg Pro Asn Glu His Asn Cys Ser Ala Ser
 945 2950 2955 2960
 Arg Arg Ile Arg Pro Glu Ser Leu Gln Gly Ala Asp His Arg Pro Tyr
 2965 2970 2975
 Thr Phe Phe Ile Ser Pro Gly Ser Arg Asp Pro Ala Gly Ser Tyr His

005000:0915550

2980	2985	2990
Leu Asn Leu Ser Ser His Phe Arg Trp Ser Ala Leu Gln Val Ser Val 2995 3000 3005		
Gly Leu Tyr Thr Ser Leu Cys Gln Tyr Phe Ser Glu Glu Asp Met Val 3010 3015 3020		
Trp Arg Thr Glu Gly Leu Leu Pro Leu Glu Glu Thr Ser Pro Arg Gln 025 3030 3035 3040		
Ala Val Cys Leu Thr Arg His Leu Thr Ala Phe Gly Ala Ser Leu Phe 3045 3050 3055		
Val Pro Pro Ser His Val Arg Phe Val Phe Pro Glu Pro Thr Ala Asp 3060 3065 3070		
Val Asn Tyr Ile Val Met Leu Thr Cys Ala Val Cys Leu Val Thr Tyr 3075 3080 3085		
Met Val Met Ala Ala Ile Leu His Lys Leu Asp Gln Leu Asp Ala Ser 3090 3095 3100		
Arg Gly Arg Ala Ile Pro Phe Cys Gly Gln Arg Gly Arg Phe Lys Tyr 105 3110 3115 3120		
Glu Ile Leu Val Lys Thr Gly Trp Gly Arg Gly Ser Gly Thr Thr Ala 3125 3130 3135		
His Val Gly Ile Met Leu Tyr Gly Val Asp Ser Arg Ser Gly His Arg 3140 3145 3150		
His Leu Asp Gly Asp Arg Ala Phe His Arg Asn Ser Leu Asp Ile Phe 3155 3160 3165		
Arg Ile Ala Thr Pro His Ser Leu Gly Ser Val Trp Lys Ile Arg Val 3170 3175 3180		
Trp His Asp Asn Lys Gly Leu Ser Pro Ala Trp Phe Leu Gln His Val 185 3190 3195 3200		
Ile Val Arg Asp Leu Gln Thr Ala Arg Ser Ala Phe Phe Leu Val Asn 3205 3210 3215		
Asp Trp Leu Ser Val Glu Thr Glu Ala Asn Gly Gly Leu Val Glu Lys 3220 3225 3230		
Glu Val Leu Ala Ala Ser Asp Ala Ala Leu Leu Arg Phe Arg Arg Leu 3235 3240 3245		
Leu Val Ala Glu Leu Gln Arg Gly Phe Phe Asp Lys His Ile Trp Leu 3250 3255 3260		
Ser Ile Trp Asp Arg Pro Pro Arg Ser Arg Phe Thr Arg Ile Gln Arg 265 3270 3275 3280		
Ala Thr Cys Cys Val Leu Leu Ile Cys Leu Phe Leu Gly Ala Asn Ala 3285 3290 3295		
Val Trp Tyr Gly Ala Val Gly Asp Ser Ala Tyr Ser Thr Gly His Val 3300 3305 3310		
Ser Arg Leu Ser Pro Leu Ser Val Asp Thr Val Ala Val Gly Leu Val 3315 3320 3325		
Ser Ser Val Val Val Tyr Pro Val Tyr Leu Ala Ile Leu Phe Leu Phe 3330 3335 3340		

Arg Met Ser Arg Ser Lys Val Ala Gly Ser Pro Ser Pro Thr Pro Ala
 345 3350 3355 3360
 Gly Gln Gln Val Leu Asp Ile Asp Ser Cys Leu Asp Ser Ser Val Leu
 3365 3370 3375
 Asp Ser Ser Phe Leu Thr Phe Ser Gly Leu His Ala Glu Gln Ala Phe
 3380 3385 3390
 Val Gly Gln Met Lys Ser Asp Leu Phe Leu Asp Asp Ser Lys Ser Leu
 3395 3400 3405
 Val Cys Trp Pro Ser Gly Glu Gly Thr Leu Ser Trp Pro Asp Leu Leu
 3410 3415 3420
 Ser Asp Pro Ser Ile Val Gly Ser Asn Leu Arg Gln Leu Ala Arg Gly
 425 3430 3435 3440
 Gln Ala Gly His Gly Leu Gly Pro Glu Glu Asp Gly Phe Ser Leu Ala
 3445 3450 3455
 Ser Pro Tyr Ser Pro Ala Lys Ser Phe Ser Ala Ser Asp Glu Asp Leu
 3460 3465 3470
 Ile Gln Gln Val Leu Ala Glu Gly Val Ser Ser Pro Ala Pro Thr Gln
 3475 3480 3485
 Asp Thr His Met Glu Thr Asp Leu Leu Ser Ser Leu Ser Ser Thr Pro
 3490 3495 3500
 Gly Glu Lys Thr Glu Thr Leu Ala Leu Gln Arg Leu Gly Glu Leu Gly
 505 3510 3515 3520
 Pro Pro Ser Pro Gly Leu Asn Trp Glu Gln Pro Gln Ala Ala Arg Leu
 3525 3530 3535
 Ser Arg Thr Gly Leu Val Glu Gly Leu Arg Lys Arg Leu Leu Pro Ala
 3540 3545 3550
 Trp Cys Ala Ser Leu Ala His Gly Leu Ser Leu Leu Val Ala Val
 3555 3560 3565
 Ala Val Ala Val Ser Gly Trp Val Gly Ala Ser Phe Pro Pro Gly Val
 3570 3575 3580
 Ser Val Ala Trp Leu Leu Ser Ser Ser Ala Ser Phe Leu Ala Ser Phe
 585 3590 3595 3600
 Leu Gly Trp Glu Pro Leu Lys Val Leu Leu Glu Ala Leu Tyr Phe Ser
 3605 3610 3615
 Leu Val Ala Lys Arg Leu His Pro Asp Glu Asp Asp Thr Leu Val Glu
 3620 3625 3630
 Ser Pro Ala Val Thr Pro Val Ser Ala Arg Val Pro Arg Val Arg Pro
 3635 3640 3645
 Pro His Gly Phe Ala Leu Phe Leu Ala Lys Glu Glu Ala Arg Lys Val
 3650 3655 3660
 Lys Arg Leu His Gly Met Leu Arg Ser Leu Leu Val Tyr Met Leu Phe
 665 3670 3675 3680
 Leu Leu Val Thr Leu Leu Ala Ser Tyr Gly Asp Ala Ser Cys His Gly
 3685 3690 3695

His Ala Tyr Arg Leu Gln Ser Ala Ile Lys Gln Glu Leu His Ser Arg
 3700 3705 3710
 Ala Phe Leu Ala Ile Thr Arg Ser Glu Glu Leu Trp Pro Trp Met Ala
 3715 3720 3725
 His Val Leu Leu Pro Tyr Val His Gly Asn Gln Ser Ser Pro Glu Leu
 3730 3735 3740
 Gly Pro Pro Arg Leu Arg Gln Val Arg Leu Gln Glu Ala Leu Tyr Pro
 745 3750 3755 3760
 Asp Pro Pro Gly Pro Arg Val His Thr Cys Ser Ala Ala Gly Gly Phe
 3765 3770 3775
 Ser Thr Ser Asp Tyr Asp Val Gly Trp Glu Ser Pro His Asn Gly Ser
 3780 3785 3790
 Gly Thr Trp Ala Tyr Ser Ala Pro Asp Leu Leu Gly Ala Trp Ser Trp
 3795 3800 3805
 Gly Ser Cys Ala Val Tyr Asp Ser Gly Gly Tyr Val Gln Glu Leu Gly
 3810 3815 3820
 Leu Ser Leu Glu Glu Ser Arg Asp Arg Leu Arg Phe Leu Gln Leu His
 825 3830 3835 3840
 Asn Trp Leu Asp Asn Arg Ser Arg Ala Val Phe Leu Glu Leu Thr Arg
 3845 3850 3855
 Tyr Ser Pro Ala Val Gly Leu His Ala Ala Val Thr Leu Arg Leu Glu
 3860 3865 3870
 Phe Pro Ala Ala Gly Arg Ala Leu Ala Ala Leu Ser Val Arg Pro Phe
 3875 3880 3885
 Ala Leu Arg Arg Leu Ser Ala Gly Leu Ser Leu Pro Leu Leu Thr Ser
 3890 3895 3900
 Val Cys Leu Leu Leu Phe Ala Val His Phe Ala Val Ala Glu Ala Arg
 905 3910 3915 3920
 Thr Trp His Arg Glu Gly Arg Trp Arg Val Leu Arg Leu Gly Ala Trp
 3925 3930 3935
 Ala Arg Trp Leu Leu Val Ala Leu Thr Ala Ala Thr Ala Leu Val Arg
 3940 3945 3950
 Leu Ala Gln Leu Gly Ala Ala Asp Arg Gln Trp Thr Arg Phe Val Arg
 3955 3960 3965
 Gly Arg Pro Arg Arg Phe Thr Ser Phe Asp Gln Val Ala His Val Ser
 3970 3975 3980
 Ser Ala Ala Arg Gly Leu Ala Ala Ser Leu Leu Phe Leu Leu Leu Val
 985 3990 3995 4000
 Lys Ala Ala Gln His Val Arg Phe Val Arg Gln Trp Ser Val Phe Gly
 4005 4010 4015
 Lys Thr Leu Cys Arg Ala Leu Pro Glu Leu Leu Gly Val Thr Leu Gly
 4020 4025 4030
 Leu Val Val Leu Gly Val Ala Tyr Ala Gln Leu Ala Ile Leu Leu Val
 4035 4040 4045
 Ser Ser Cys Val Asp Ser Leu Trp Ser Val Ala Gln Ala Leu Leu Val

4050 4055 4060
 Leu Cys Pro Gly Thr Gly Leu Ser Thr Leu Cys Pro Ala Glu Ser Trp
 065 4070 4075 4080
 His Leu Ser Pro Leu Leu Cys Val Gly Leu Trp Ala Leu Arg Leu Trp
 4085 4090 4095
 Gly Ala Leu Arg Leu Gly Ala Val Ile Leu Arg Trp Arg Tyr His Ala
 4100 4105 4110
 Leu Arg Gly Glu Leu Tyr Arg Pro Ala Trp Glu Pro Gln Asp Tyr Glu
 4115 4120 4125
 Met Val Glu Leu Phe Leu Arg Arg Leu Arg Leu Trp Met Gly Leu Ser
 4130 4135 4140
 Lys Val Lys Glu Phe Arg His Lys Val Arg Phe Glu Gly Met Glu Pro
 145 4150 4155 4160
 Leu Pro Ser Arg Ser Ser Arg Gly Ser Lys Val Ser Pro Asp Val Pro
 4165 4170 4175
 Pro Pro Ser Ala Gly Ser Asp Ala Ser His Pro Ser Thr Ser Ser Ser
 4180 4185 4190
 Gln Leu Asp Gly Leu Ser Val Ser Leu Gly Arg Leu Gly Thr Arg Cys
 4195 4200 4205
 Glu Pro Glu Pro Ser Arg Leu Gln Ala Val Phe Glu Ala Leu Leu Thr
 4210 4215 4220
 Gln Phe Asp Arg Leu Asn Gln Ala Thr Glu Asp Val Tyr Gln Leu Glu
 225 4230 4235 4240
 Gln Gln Leu His Ser Leu Gln Gly Arg Arg Ser Ser Arg Ala Pro Ala
 4245 4250 4255
 Gly Ser Ser Arg Gly Pro Ser Pro Gly Leu Arg Pro Ala Leu Pro Ser
 4260 4265 4270
 Arg Leu Ala Arg Ala Ser Arg Gly Val Asp Leu Ala Thr Gly Pro Ser
 4275 4280 4285
 Arg Thr Pro Leu Arg Ala Lys Asn Lys Val His Pro Ser Ser Thr
 4290 4295 4300

<210> 3
 <211> 12685
 <212> DNA
 <213> C. Elegans lov-1 gene

<400> 3
 tcaatctttc tccacatcgt ttagccgccca cttctggaat ctcttttggtc cagtttcgtg 60
 aatagcagag acaggatcat aggagagtgt gtagttgatg actgttttgtt tttggtattg 120
 accttgagtt tggagcattc tgggtggcacg atgatgaagc agattgactt tggcaacagc 180
 gctgtggaat agacggaagt cttttttgagt gtcagcaatt gaaactggag caaaatcttt 240
 tggttcaaga agacccaagc gacgttttgt ctgaaattaa ataacagaaa ttaaagaaca 300
 tctaatagtg agcttgaaaa ataaatacct tgtattttat gtgatcgatt atttcgtaat 360
 cattgggtctg cttctcactg tcattacgaa tttcctcgaa ctcgaaacata attatagtga 420

acatatcaaa gttatccaca taagttctcg ggtttgtggc atagcaaact aatccaactt 4500
gaatcagtgt tttatctgtg atctcagcag tattcagagt tgaagcgggc gatggaagtt 4560
tgaatgccca ttcttcacag ttttgagttt ttcttacaat atttgatgca tcatcgataa 4620
cgattacat tccggttccg tcgacgctat tctaaaaatt tgattgacat tagtgtaaac 4680
tgtaactttt tgattaccga gtagtcataa ggtaagttgc cagttgctat agctctagct 4740
gctagcgtgt tttccagggt atctagtgtg gatgcaagtt ggttggctag atttttggcc 4800
tgaatagaat atgaataatt ccaaactcaa aaagttttta aaactcacga tgttcttctg 4860
gaacattttt gtgacgtaag cagcccatc ttctgacgtc atttctcca cgtacacaat 4920
attgtctgga tcaactggga gcacgttgta caaggaatca tagttatctg ttgcatattt 4980
caaattggca gctagatcag aagaaagagg attgtcgaga gcaatcttca acgctgatgt 5040
taaagatccc gcaattgaaa ggagagagtt ggatgtctga aaattattat tatgacatct 5100
accaaagttt agtgtatgaa tacatcatta atctctgcat ctgtcatagt cattccatta 5160
tttgtaagaa aatcttgagt attgctaaga atcgtttcaa tttgttgctg ggattcttga 5220
ttcatcaaac tttgcggcac aatatctgga tatttaaaat gatttgtatg catttgtgta 5280
tttatttttt tgagttacca attttagttc ccgaaacatc gccttcctgc gaaacttgtc 5340
cattctgaat tacatatcca ttcgttccat ttctaataat caaccctcca tcgattctca 5400
ttttctgtgt gtcagagaat tccattaaag ttctcaaaat taaagttcct atacaaaata 5460
tccattcgag actatactta caccgtatga gtttgagaac cagatgtgta agttccggct 5520
gttatctgaa taaccgaacc tccaagcgcc aaagaaacaa tattgtaggt gggagaactg 5580
atcaccagag ttgtcacaga gtttgacaaa taaagggcgg tggagtctac gaaaaatgag 5640
tagccgctga catcgatgga tgacgctttg gagaagaata gctgcaagaa aagttatttt 5700
gatattaaca actcatcagc aaaagtctta cagttcccga aacggtgaca agtgtttgtt 5760
ccttaatcaa tgattgcaaa tcatctttgg tgtacgaagc cgtcggtgaa agagtagata 5820
ttgagacagt ttgagataaa gcagagacag ctggaattcc aatgtcctgc ggagacagca 5880
ccattcgcat tgaataactt cccgcgtttg agaacacaag tggagaagta gtttgattga 5940
ataaagcaag gttgacgtct gaaattttta gcgtcataac cagaccactc ccattgcata 6000
cttactctca ataactatcg gcatctgaat caacttctta accgtgctcg ctgaggatcc 6060
atctgatgcc acaaccgtga agctgtcagc attgtatgag aaaatggcat tatctgtgtc 6120
tacttcaaca aactttcctg ttccattcgt gcaagttatt gtgtaagtaa ctccaccata 6180
tgatgcagtt actactagtc ctctagatac aatattttga gtagaatgca gttttatcat 6240
tgttccagat tcaatctgaa taaaaattga aaaatttcat gtgctctacg atttataaat 6300
ttaccaataa tatgtattga acttctgaga ctgggatatt gaacgaaaat gaagtgttct 6360
tctgacttgt ggatcctact gttgaattgt cataagtgac attccaagca gttacataca 6420

atcgtgtaga aaatgatatc aactaccgga aaagtagttt tccgactcat atttccatgg 8520
 agtacaaaaa gcactcccta gtaggcaaaa tctcacactc tgtcaagcaa ttgctttcct 8580
 tcagtaaaac aaatggctga gaagaatcgt ttcgacattg acaggtcata gcagtcttaa 8640
 aatattaagg ttttttttaa gtaagattga tttgaatata ttaccgttaa agctccgggc 8700
 tctttgtttg gaattgggtg aatataaaat ggattttcag agtaatacac tgtctcggtc 8760
 catgtcaaata tttccaatac aaagtcgtaa ggggtttctg tacttgcgtc tggatccaca 8820
 gttgttggtc tcatgctatc agatgcactt gatgaatcgg atgggtgttg agataaacca 8880
 gatgaatctg aagtggatgg agttgagtta gatgagtcta tgggtgggga atctgaagtt 8940
 gtgccagaat ccgatgttga tgtagaactg tcttgtgaag catcagtcgt gctagcttcc 9000
 aaagtcgacg tagattcaat tcttgaagtt gtggaaatgg ctgaactttc ggaagaagat 9060
 ccagttgaag ttgtactggg aacttcggat gtacttggtg aatccgcaac aacattcaat 9120
 gtgaaaatgt ggctgaccac ttgcattgtc gtcaaatccg tcatgttgat tcgaaactca 9180
 taggtgccaa tgccaacaag aaatgtttca attgggtgaa ttggaatatt agaagaataa 9240
 gttgcgttta ggaccgtgtt tgettgaaat tgcgtttaat tcaataattt caaaaagttt 9300
 gttaatacta cagtagttta agcaagtggg ttccttaatt ataagaaaag gctcagtaga 9360
 cacatttctg cattcaaatg tttggcttct ctaaaatcat tcgtttcatt tggctcaacg 9420
 atttattaaa cccgcctcag taggagtaat ggcattagtt ggtaaaggta caatgttgat 9480
 gctgtcttca ttgtgacgtg tctcgttcca tgacaatcca ctgtccaaga tgaaatcgaa 9540
 ctgatcgact gacaaagtgg aagttgaatc agcagtggta gaactcggac tggaagaagt 9600
 tgtggatgtg tccgagatgg tagttgtact ggaatcagta gtactttctt cggaagttgt 9660
 tgtggattct tgtaaagtag ttgtgctccc agccgacgtt gtcgtagaat cgcttgaacg 9720
 tgtggatgac ggctctgtga ctgtggatgt tgataatgtg gaagatggag ttgatgggtg 9780
 agatgacgta gagcttgcta cagcagatgt agaagattcc gactctatgg tgggtggaaga 9840
 atattcctga atataaacgt tcgcatacgt gtagtaaaact tttttatcgt cggttgtcat 9900
 agttgctctg aagggtgtagt ttccaggacc aacgaatgtg ctagcagggg acgtccctcc 9960
 gagacgtggc attgatacac tttctgaata tattgaaaaa atatgtgtaa aaaatctaaa 10020
 taactatcgc ccgaaaaagg tttgcttttt ttccgatttg aagtttttat agaaacgttt 10080
 tcagaattaa agattttgcc tgtctctaata ttataataag tctttataaa caattactcg 10140
 tgaaacatgc tccgtcttta gtgggtgaaa cataattaga agatgtaggg cttgtacatt 10200
 cgatggatgt ttgatactga aatacagtgt tacatttgaa taatgcagtc ttcaatattg 10260
 tacttactcc aatgattccg aggccggaat taagcgtag gttcacactt gtggaatcat 10320
 agaacgttgt agttgccttt tctacaaaat agaagtctgg attagttccg tccgagctag 10380
 tagttgtctc agattttgtt gttgttgaac tttgctgagt agacgtggat gattgagtag 10440

			245						250						255		
Arg	Met	Lys	Arg 260	Asp	Ala	Gly	Asp	Asn 265	Thr	Cys	Asp	Tyr	Thr 270	Ile	Glu		
Ser	Thr	Ser 275	Thr	Ser	Thr	Thr	Thr 280	Pro	Thr	Thr	Thr	Thr 285	Val	Thr	Ser		
Thr	Val 290	Thr	Ser	Thr	Thr	Thr 295	Val	Pro	Thr	Ser	Thr 300	Ser	Thr	Val	Thr		
Thr 305	Ala	Met	Ser	Thr	Ser 310	Thr	Ser	Thr	Pro	Ser 315	Thr	Ser	Thr	Thr	Ile 320		
Glu	Ser	Thr	Ser	Thr 325	Thr	Phe	Thr	Ser	Thr 330	Ala	Ser	Thr	Ser	Thr 335	Ser		
Ser	Thr	Ser	Thr 340	Thr	Gln	Gln	Ser	Ser 345	Ser	Thr	Ile	Thr	Ser 350	Ser	Pro		
Ser	Ser	Thr 355	Thr	Leu	Ser	Thr	Ser 360	Ile	Pro	Thr	Thr 365	Thr	Thr	Pro	Glu		
Ile	Thr 370	Ser	Thr	Leu	Ser	Ser 375	Leu	Pro	Asp	Asn	Ala 380	Ile	Cys	Ser	Tyr		
Leu 385	Asp	Glu	Thr	Thr	Thr 390	Ser	Thr	Thr	Phe	Thr 395	Thr	Thr	Met	Leu	Thr 400		
Ser	Thr	Thr	Thr	Glu 405	Glu	Pro	Ser	Thr	Ser 410	Thr	Thr	Thr	Thr	Glu 415	Val		
Thr	Ser	Thr	Ser 420	Ser	Thr	Val	Thr	Thr 425	Thr	Glu	Pro	Thr 430	Thr	Thr	Leu		
Thr	Thr	Ser 435	Thr	Ala	Ser	Thr	Ser 440	Thr	Thr	Glu	Pro	Ser 445	Thr	Ser	Thr		
Val	Thr 450	Thr	Ser	Pro	Ser	Thr 455	Ser	Pro	Val	Thr	Ser 460	Thr	Val	Thr	Ser		
Ser 465	Ser	Ser	Ser	Ser	Thr 470	Thr	Val	Thr	Thr	Pro 475	Thr	Ser	Thr	Glu	Ser 480		
Thr	Ser	Thr	Ser	Pro 485	Ser	Ser	Thr	Val	Thr 490	Thr	Ser	Thr	Thr	Ala 495	Pro		
Ser	Thr	Ser	Thr 500	Thr	Gly	Pro	Ser	Ser 505	Ser	Ser	Ser	Thr	Pro 510	Ser	Ser		
Thr	Ala 515	Ser	Ser	Ser	Val	Ser 520	Ser	Thr	Ala	Ser	Ser 525	Thr	Gln	Ser	Ser		
Thr	Ser 530	Thr	Gln	Gln	Ser	Ser 535	Thr	Thr	Thr	Lys	Ser 540	Glu	Thr	Thr	Thr		
Ser 545	Ser	Asp	Gly	Thr	Asn 550	Pro	Asp	Phe	Tyr	Phe 555	Val	Glu	Lys	Ala	Thr 560		
Thr	Thr	Phe	Tyr 565	Asp	Ser	Thr	Ser	Val	Asn 570	Leu	Thr	Leu	Asn	Ser 575	Gly		
Leu	Gly	Ile	Ile 580	Gly	Tyr	Gln	Thr	Ser 585	Ile	Glu	Cys	Thr	Ser 590	Pro	Thr		
Ser	Ser	Asn	Tyr	Val	Ser	Thr	Thr	Lys	Asp	Gly	Ala	Cys	Phe	Thr	Lys		

009060:0975960

945		950		955		960
Arg Thr Thr Thr Val	Asp Pro Asp Ala Ser Thr Glu Thr Pro Tyr Asp					
	965			970		975
Phe Val Leu Glu Asn Leu Thr Trp Asn Glu Thr Val Tyr Tyr Ser Glu						
	980			985		990
Asn Pro Phe Tyr Ile Thr Pro Ile Pro Asn Lys Glu Pro Gly Ala Leu						
	995			1000		1005
Thr Thr Ala Met Thr Cys Gln Cys Arg Asn Asp Ser Ser Gln Pro Phe						
	1010			1015		1020
Val Leu Leu Lys Glu Ser Asn Cys Leu Thr Glu Phe Gly Lys Asn Gly						
1025				1030		1035
Ala Tyr Ser Ala Ser Val Ser Phe Asn Pro Met Thr Ser Phe Val Pro						
	1045			1050		1055
Ala Thr Gly Thr Tyr Glu Phe Leu Ile Asn Val Thr Asn Arg Ala Ser						
	1060			1065		1070
Gly Glu Ser Ala Ser His Ile Phe Thr Met Asn Val Val Leu Pro Thr						
	1075			1080		1085
Thr Thr Thr Glu Thr Pro Pro Thr Thr Val Ser Ser Ser Asp Asp Ala						
	1090			1095		1100
Gly Gly Lys Thr Gly Gly Thr Gly Ala Thr Gly Gly Thr Gly Gly Thr						
1105				1110		1115
Gly Ser Gly Gly Ser Ala Thr Thr Leu Ser Thr Gly Asp Ala Val Arg						
	1125			1130		1135
Ser Thr Thr Ser Gly Ser Gly Ser Gly Gln Ser Ser Thr Gly Ser Gly						
	1140			1145		1150
Ala Gly Gly Ser Gly Thr Thr Ala Ser Gly Ser Gly Ser Gly Gly Ser						
	1155			1160		1165
Ser Gly Thr Gly Ser Asp Gly Val Asn Ser Gly Lys Thr Thr Ala Leu						
	1170			1175		1180
Asn Gly Asp Gly Thr Gly Ser Gly Thr Ala Thr Thr Pro Gly Ser His						
1185				1190		1195
Leu Gly Asp Gly Gly Ser Thr Ser Gly Ser Gly Ser Asp Ser Asn Gly						
	1205			1210		1215
Ser Ser Gly Val Ser Thr Lys Ser Ser Ser Gly Ser Asp Thr Ser Gly						
	1220			1225		1230
Ser Ser Asp Ser Ser Gly Ala Asn Gly Ala Phe Ser Ala Thr Ala Gln						
	1235			1240		1245
Pro Ser Thr Arg Thr Thr Lys Thr Arg Ser Ser Leu Ala Thr Val Ser						
	1250			1255		1260
Pro Ile Ser Ala Ala Glu Gln Ala Ile Ile Asp Ala Gln Lys Ala Asp						
1265				1270		1275
Val Met Asn Gln Leu Ala Gly Ile Met Asp Gly Ser Ala Ser Asn Asn						
	1285			1290		1295
Ser Leu Asn Thr Ser Ser Ser Leu Leu Asn Gln Ile Ser Ser Leu Pro						

1300	1305	1310
Ala Ala Asp Leu Val Glu Val Ala Gln Ser Leu Leu Ser Asn Thr Leu 1315 1320 1325		
Lys Ile Pro Gly Val Gly Asn Met Ser Ser Val Asp Val Leu Lys Thr 1330 1335 1340		
Leu Gln Asp Asn Ile Ala Thr Thr Asn Ser Glu Leu Ala Asp Glu Met 1345 1350 1355 1360		
Ala Lys Val Ile Thr Lys Leu Ala Asn Val Asn Met Thr Ser Ala Gln 1365 1370 1375		
Ser Leu Asn Ser Val Leu Ser Ser Leu Asp Leu Ala Leu Lys Gly Ser 1380 1385 1390		
Thr Val Tyr Thr Leu Gly Val Ser Ser Thr Lys Ser Lys Asp Gly Thr 1395 1400 1405		
Tyr Ala Val Ile Phe Gly Tyr Val Ile Ala Ser Gly Tyr Thr Leu Val 1410 1415 1420		
Ser Pro Arg Cys Thr Leu Ser Ile Tyr Gly Ser Thr Ile Tyr Leu Thr 1425 1430 1435 1440		
Gly Asp Thr Arg Ala Ser Tyr Lys Gln Leu Asp Gly Asp Thr Val Thr 1445 1450 1455		
Ala Asp Thr Met Leu Ala Ala Ala Ile Gly Ile Gln Gly Met Phe Ala 1460 1465 1470		
Thr Asn Gly Arg Thr Val Gln Val Glu Gln Asp Lys Ile Asp Asp Lys 1475 1480 1485		
Arg Ser Leu Val Ser Gly Asn Ile Met Ala Thr Met Ser Gly Val Gly 1490 1495 1500		
Asp Val Gln Ser Gly Glu Tyr Ser Tyr Asn Asp Met Tyr Val Thr Ala 1505 1510 1515 1520		
Trp Asn Val Thr Tyr Asp Asn Ser Thr Val Gly Ser Thr Ser Gln Lys 1525 1530 1535		
Asn Thr Ser Phe Ser Phe Asn Ile Pro Val Ser Glu Val Gln Tyr Ile 1540 1545 1550		
Leu Leu Ile Glu Ser Gly Thr Met Ile Lys Leu His Ser Thr Gln Asn 1555 1560 1565		
Ile Val Ser Arg Gly Leu Val Val Thr Ala Ser Tyr Gly Gly Val Thr 1570 1575 1580		
Tyr Thr Ile Thr Cys Thr Asn Gly Thr Gly Lys Phe Val Glu Val Asp 1585 1590 1595 1600		
Thr Asp Asn Ala Ile Phe Ser Tyr Asn Ala Asp Ser Phe Thr Val Val 1605 1610 1615		
Ala Ser Asp Gly Ser Ser Ala Ser Thr Val Lys Lys Leu Ile Gln Met 1620 1625 1630		
Pro Ile Val Ile Glu Asn Val Asn Leu Ala Leu Phe Asn Gln Thr Thr 1635 1640 1645		
Ser Pro Leu Val Phe Ser Asn Ala Gly Ser Tyr Ser Met Arg Met Val 1650 1655 1660		

Leu Ser Pro Gln Asp Ile Gly Ile Pro Ala Val Ser Ala Leu Ser Gln
 1665 1670 1675 1680
 Thr Val Ser Ile Ser Thr Leu Ser Pro Thr Ala Ser Tyr Thr Lys Asp
 1685 1690 1695
 Asp Leu Gln Ser Leu Ile Lys Glu Gln Thr Leu Val Thr Val Ser Gly
 1700 1705 1710
 Thr Thr Ser Asn Ser Leu Leu Ser Ile Ala Gly Ser Leu Thr Ser Ala
 1715 1720 1725
 Leu Lys Ile Ala Leu Asp Asn Pro Leu Ser Ser Asp Leu Ala Ala Asn
 1730 1735 1740
 Leu Lys Tyr Ala Thr Asp Asn Tyr Asp Ser Leu Tyr Asn Val Leu Pro
 1745 1750 1755 1760
 Ser Asp Pro Asp Asn Ile Val Tyr Val Glu Glu Met Thr Ser Glu Glu
 1765 1770 1775
 Trp Ala Ala Tyr Val Thr Lys Met Phe Gln Lys Asn Ile Ala Lys Asn
 1780 1785 1790
 Leu Ala Asn Gln Leu Ala Ser Thr Leu Asp Thr Leu Glu Asn Thr Leu
 1795 1800 1805
 Ala Ala Arg Ala Ile Ala Thr Gly Asn Leu Pro Tyr Asp Tyr Ser Asn
 1810 1815 1820
 Ser Val Asp Gly Thr Gly Met Val Ile Val Ile Asp Asp Ala Ser Asn
 1825 1830 1835 1840
 Ile Val Gly Lys Thr Gln Asn Cys Glu Glu Trp Ala Phe Lys Leu Pro
 1845 1850 1855
 Ser Pro Ala Ser Thr Leu Asn Thr Ala Glu Ile Thr Asp Lys Thr Leu
 1860 1865 1870
 Ile Gln Val Gly Leu Val Cys Tyr Ala Thr Asn Pro Arg Thr Tyr Val
 1875 1880 1885
 Asp Asn Phe Asp Met Leu Ile Thr Ser Gly Ala Leu Glu Ala His Ile
 1890 1895 1900
 Lys Asp Glu Asn Gln Ile Ile Ile Pro Ile Thr Gly Thr Thr Ala Pro
 1905 1910 1915 1920
 Ile Tyr Val Asn Gly Arg Gly Ser Glu Asp Asp Ala Val Leu Thr Leu
 1925 1930 1935
 Met Gln Gln Gly Asp Phe Ala Ser Tyr Gln Ile Leu Asp Leu His Ala
 1940 1945 1950
 Phe Arg Thr Thr Asn Trp Asn Asn Ser Leu Gln Val Glu Ile Ile Ala
 1955 1960 1965
 Ser Gln Asp Tyr Glu Ile Pro Asn Asn Asp Asp Thr Tyr Met Phe Ser
 1970 1975 1980
 Ser Phe Gln Ser Leu Pro Gly Pro Leu Glu Ser Asn His Glu Trp Ile
 1985 1990 1995 2000
 Phe Asp Leu Asn Thr Leu Asn Lys Thr Ser Asn Tyr Phe Val Thr Ala
 2005 2010 2015

Gly Asn Leu Ile Asn Asn Thr Gly Leu Phe Phe Ile Gly Ile Gly Lys
 2020 2025 2030
 Arg Asn Ser Ser Thr Asn Thr Gly Asn Ser Ser Asp Ile Val Asn Tyr
 2035 2040 2045
 Gly Gln Tyr Asp Ser Met Gln Trp Ser Phe Ala Arg Ser Val Pro Met
 2050 2055 2060
 Asp Tyr Gln Val Ala Ala Val Ser Lys Gly Cys Tyr Phe Tyr Gln Lys
 2065 2070 2075 2080
 Thr Ser Asp Val Phe Asn Ser Glu Gly Met Tyr Pro Ser Asp Gly Gln
 2085 2090 2095
 Gly Met Gln Phe Val Asn Cys Ser Thr Asp His Leu Thr Met Phe Ser
 2100 2105 2110
 Val Gly Ala Phe Asn Pro Thr Ile Asp Ala Asp Phe Ser Tyr Asn Tyr
 2115 2120 2125
 Asn Val Asn Glu Ile Glu Lys Asn Val Lys Val Met Ile Ala Ala Val
 2130 2135 2140
 Phe Met Leu Val Val Tyr Gly Cys Leu Thr Ile Asn Ala Ile Ile Cys
 2145 2150 2155 2160
 Gln Arg Lys Asp Ala Ser Arg Gly Arg Leu Arg Phe Leu Lys Asp Asn
 2165 2170 2175
 Glu Pro His Asp Gly Tyr Met Tyr Val Ile Ala Val Glu Thr Gly Tyr
 2180 2185 2190
 Arg Met Phe Ala Thr Thr Asp Ser Thr Ile Cys Phe Asn Leu Ser Gly
 2195 2200 2205
 Asn Glu Gly Asp Gln Ile Phe Arg Ser Phe Arg Ser Glu Glu Asp Gly
 2210 2215 2220
 Asn Trp Glu Phe Pro Phe Ser Trp Gly Thr Thr Asp Arg Phe Val Met
 2225 2230 2235 2240
 Thr Thr Ala Phe Pro Leu Gly Glu Leu Glu Tyr Met Arg Leu Trp Leu
 2245 2250 2255
 Asp Asp Ala Gly Leu Asp His Arg Glu Ser Trp Tyr Cys Asn Arg Ile
 2260 2265 2270
 Ile Val Lys Asp Leu Gln Thr Gln Asp Ile Tyr Tyr Phe Pro Phe Asn
 2275 2280 2285
 Asn Trp Leu Gly Thr Lys Asn Gly Asp Gly Glu Thr Glu Arg Leu Ala
 2290 2295 2300
 Arg Val Glu Tyr Lys Arg Arg Phe Leu Asp Glu Ser Met Ser Met His
 2305 2310 2315 2320
 Met Leu Ala Gln Thr Ile Ser Trp Phe Ala Met Phe Thr Gly Gly Gly
 2325 2330 2335
 Asn Arg Leu Arg Asp Arg Val Ser Arg Gln Asp Tyr Ser Val Ser Ile
 2340 2345 2350
 Ile Phe Ser Leu Val Val Val Ser Met Ile Ser Ile Thr Ile Leu Lys
 2355 2360 2365
 Ser Asp Asn Ser Ile Ile Ser Asp Ser Lys Ser Val Ser Glu Phe Thr

2380

[illegible]

				2725					2730							2735
Thr	Glu	Thr	Val	Ser	Gly	Leu	Leu	Tyr	Ser	Tyr	Ser	Gly	Gly	Gly	Tyr	
			2740					2745					2750			
Thr	Ile	Ser	Met	Ser	Gly	Thr	Gln	Ala	Glu	Ile	Ile	Thr	Leu	Phe	Asn	
		2755					2760					2765				
Lys	Leu	Asp	Ser	Glu	Arg	Trp	Ile	Asp	Asp	His	Thr	Arg	Ala	Val	Ile	
	2770					2775					2780					
Ile	Glu	Phe	Ser	Ala	Tyr	Asn	Ala	Gln	Ile	Asn	Tyr	Phe	Ser	Val	Val	
2785					2790					2795					2800	
Gln	Leu	Leu	Val	Glu	Ile	Pro	Lys	Ser	Gly	Ile	Tyr	Leu	Pro	Asn	Ser	
			2805						2810					2815		
Trp	Val	Glu	Ser	Val	Arg	Leu	Ile	Lys	Ser	Glu	Gly	Ser	Asp	Gly	Thr	
			2820					2825					2830			
Val	Val	Lys	Tyr	Tyr	Glu	Met	Leu	Tyr	Ile	Phe	Phe	Ser	Val	Leu	Ile	
		2835					2840					2845				
Phe	Val	Lys	Glu	Ile	Val	Phe	Tyr	Leu	Tyr	Gly	Arg	Tyr	Lys	Val	Ile	
	2850					2855					2860					
Thr	Thr	Met	Lys	Pro	Thr	Arg	Asn	Pro	Phe	Lys	Ile	Val	Tyr	Gln	Leu	
2865					2870					2875					2880	
Ala	Leu	Gly	Asn	Phe	Ser	Pro	Trp	Asn	Phe	Met	Asp	Leu	Ile	Val	Gly	
			2885						2890					2895		
Ala	Leu	Ala	Val	Ala	Ser	Val	Leu	Ala	Tyr	Thr	Ile	Arg	Gln	Arg	Thr	
			2900					2905					2910			
Thr	Asn	Arg	Ala	Met	Glu	Asp	Phe	Asn	Ala	Asn	Asn	Gly	Asn	Ser	Tyr	
		2915					2920					2925				
Ile	Asn	Leu	Thr	Glu	Gln	Arg	Asn	Trp	Glu	Ile	Val	Phe	Ser	Tyr	Cys	
	2930					2935					2940					
Leu	Ala	Gly	Ala	Val	Phe	Phe	Thr	Ser	Cys	Lys	Met	Ile	Arg	Ile	Leu	
2945					2950					2955					2960	
Arg	Phe	Asn	Arg	Arg	Ile	Gly	Val	Leu	Ala	Thr	Leu	Asp	Asn	Ala		
			2965						2970					2975		
Leu	Gly	Ala	Ile	Val	Ser	Phe	Gly	Ile	Ala	Phe	Leu	Phe	Phe	Ser	Met	
			2980					2985					2990			
Thr	Phe	Asn	Ser	Val	Leu	Tyr	Ala	Val	Leu	Gly	Asn	Lys	Met	Gly	Gly	
		2995					3000					3005				
Tyr	Arg	Ser	Leu	Met	Ala	Thr	Phe	Gln	Thr	Ala	Leu	Ala	Gly	Met	Leu	
	3010					3015					3020					
Gly	Lys	Leu	Asp	Val	Thr	Ser	Ile	Gln	Pro	Ile	Ser	Gln	Phe	Ala	Phe	
3025					3030					3035					3040	
Val	Val	Ile	Met	Leu	Tyr	Met	Ile	Ala	Gly	Ser	Lys	Leu	Val	Leu	Gln	
			3045						3050					3055		
Leu	Tyr	Val	Thr	Ile	Ile	Met	Phe	Glu	Phe	Glu	Glu	Ile	Arg			

3075

3080

3085

Lys Thr Lys Arg Arg Leu Gly Leu Leu Glu Pro Lys Asp Phe Ala Pro
 3090 3095 3100

Val Ser Ile Ala Asp Thr Gln Lys Asp Phe Arg Leu Phe His Ser Ala
 3105 3110 3115 3120

Val Ala Lys Val Asn Leu Leu His His Arg Ala Thr Arg Met Leu Gln
 3125 3130 3135

Thr Gln Gly Gln Tyr Gln Asn Gln Thr Val Ile Asn Tyr Thr Leu Ser
 3140 3145 3150

Tyr Asp Pro Val Ser Ala Ile His Glu Thr Gly Pro Lys Arg Phe Gln
 3155 3160 3165

Lys Trp Arg Leu Asn Asp Val Glu Lys Asp
 3170 3175

<210> 5

<211> 8073

<212> DNA

<213> C. Elegans *pkd-2* gene

<400> 5

tcattcttct tttttgtcag caatcgaggt gattggtgga cgacgagcgg cagattcacg 60
 gttacggact tggttggtga ggagggcctg gacaagtaaa atattttattg gaaatttaga 120
 tatttagcag taacagcaaa attatttgta ttttggtgtt taatttacta aatagtaaaa 180
 attgtaagtt ttcattaatt cttattgcca gaataaaaaa ttttctaatt ttgttttgtc 240
 taatttgtct aaaactacga aagtttttct ctaaaaattt cactagataa atacaatttt 300
 tcatgtttca attactttcc aaaagaagta acactataat tgcattagtt acaattttca 360
 actcacactc aaatccatca aatttcctcc atcttggtgt tgaactcttt gtttttcgat 420
 tgtctggagt gttgcattga ctcttccaat ccgatccaca atgctgaaca ctgattcttg 480
 catttgatct acacggcggt tcaaaactgaa atgatttacg taatgtttat gatcatttat 540
 gatagagctg atacagtaaa agttaccaat ttttgtttct attcttcgga attgtgaaaa 600
 aatacaattt tctcatgggt ttcattattt gaaaattcca gtcttcacac gtataaaactg 660
 gaacacgaaa aactatgggt tttattctag aatactaatt ttttaatcga taaataatat 720
 tatcgtcaaa aaagcataaa gttttttttg taagatatat gaaaatcgaa taacaaaagt 780
 taaacttaat caatttatga aaacattgaa ccagtcaaaa atctaattgt gataccgtga 840
 aaaaaaacg tttccctcca aaagtttacc tttttcaagt cttctgttaa caaattttca 900
 gaacgtttat atttgatatg tgacgggtgaa acattatttg atcaaaaactg ctgtgggaac 960
 tgacggttat tatataatta aggttattat ggtaacagtg aaacagtatt taaaaatagc 1020
 tgtttcggta ctcaaggggt atcccatgag gaaaataaaa gtattacttt ttcagttatg 1080
 aaaactgaga atgttttcac aaaatgttac ctgtggtctg tttgggaaaa aggaaatcta 1140
 cgatgagaaa tttgcagaac attttttgtc aaaattctct acatgttttt ttttggtgta 1200

gtggagacgg tgacggccga tagcaaaaag ctctcgaaa atgaagtata gtatgaatcc 3300
acagaagatt ccttcaaaaa tcatcattcg ggtgcctcca gatgtttgat aggtcagaag 3360
atcgtaagtc ataagctttg gagttgtgat aacaccgcca gatgcaggga gctcaaatag 3420
gagtctgaaa tgggaaatth cgaaaaaaat ttaactcgct gcttcagctt tatcataaaa 3480
ttggcgact tatttgaaaa ttattatctg atcgacattg attggaatgc aaatatttat 3540
aataaatttg ttgacgtaac taaagtttaa aaatccagtt taaaaaaact atgtaaaatt 3600
tcagtactct tgaaactaga caagatttat acttgttttc atttccatag acaccctcac 3660
agttggccgg gtgactgata tgtatggccc gacatthttc gggttactgt ggattcatag 3720
thttcggtgt ggccattgc aaggcaaagc tagtgccggc cgaaactcg aaaacgtcg 3780
accatgcata tcagtcaaat gccactcgaa thtcgaaatt ttgaaatgaa cgtttactct 3840
tgttgaaata cttataatta cagthtcaca aacattgtaa aattthtagtc aaaaacgaga 3900
caccattcca ccaaacatga tagaactcac thcaccacac aaaacagatt aatattcgca 3960
ttgtacagag caaagtccac aataattgca cgtgatctc tgcgatcca gcgattagcc 4020
thtaacgtgg caattgcaga ttgagcttca gttgagccag ctactggaag gcgttgaaca 4080
aatccaccac ctccatatga agcaatggcg ccacggtht tcaggththt aagctcttht 4140
gccgtggcgt agatgaatct gaatataata thttattthaa aaaaaggatt ggtgagactg 4200
thththtatag gaattatatg ttgacaataa ctatctaaga ctaacaatta aatgaaaatt 4260
gcatgacaac cataatgttc taaaattthaa aaaaaggagc atgaaacatt acgaatatta 4320
gttagaatat thcaatttht gaggtactth tcacaaactt tacattthth tcaacgttht 4380
thtaataagaa tactctthtca ggtagttaat atataagcta aattthtgcatt ttgtgtattg 4440
aagctththt aaaaacacat aaacagatat aactgataat thcttggaac ataaaattgt 4500
attthtcatgc aaatttcgta acattcttht aaatacagtt tcataatatt gthtaaaaaga 4560
aattgggggt thctcaatag thcataaaat thtaaatatt thtaaaataa aactaagtat 4620
. thtccgcaa taagtcaagt thtgcaataa aattthactgt thcacattat gatcaagtht 4680
gcatcacaat aagaaataat agtaaaaatt ggtthtccat gaaaaaaccc cataaatgcc 4740
atgaaacaac gttagctccg cththcacca atcgccgatt ggtcagcaga attcaaaagg 4800
tactagaagc tgctgattca acgaccaaac ttggccgaat thacaaaatt gacgtcactc 4860
acgcatcaac acttccatca ccgaccatcg thttatctc gagctththt tcataatttg 4920
caaaacattc cttaatctcc cgctggaaac ththtcatcac agtacacgag tcatttgthca 4980
ctthcaacat thtgatccga ggtthcccaa gcaaacgatt thcatagtag atcatattct 5040
cgthtatccgt cgaattggaa gththcgtcc aatatatgcc aggtattagg acttgthgaca 5100
gccactgaaa gthtgatttg aaggththtca thtaaaaatt gaggaactt acatcccaaa 5160
tattatccat tgaggtaaaa gatccaaatg ctggagctcc ggaggcaccg gtgctcgcca 5220

caaacaggtc gctcattact ttggagtagt agtaagattg gatgctgttt tgggcgaacg 5280
 caactgtaaa tttttgaatt tagaaaaaaa aaacccgtga agtgtcgggt gctaactggg 5340
 cgtgctcgat atatcacagg attagcccga ctacctgcga ggtgtcgcgc gaaacactag 5400
 atgaaaattt tacaagaaaa tgattttcga aaatacaaac atttgttaac attaattgta 5460
 tttttaagtt gtaaacgcaa aaataaatat tggaaatttg aaaatgtttt gttacaaaaa 5520
 ttctgctgtt ttgcttacta agtaaaccta acaaattata ggtaaaaaata gtatgtgaac 5580
 gtttcatgag gttattcaag tagtgtcgga aaattaaaaa gtgtagaaaa attacgtcac 5640
 aactgtatta aaatacataa aaacatgtat ttttaatacat ttgtgacgtc acaaatgtat 5700
 ttaaatacat tttgctacat tacttgatta accccattaa caaagttgta ctcgtaaaat 5760
 ttcagttgaa atgctcaaac tcactaaacg tgttgaggaa aaaaaataaa aatttaaaaa 5820
 aaaactgttc caccgttgta acaaatgttg tacgcgtttg tcttaaatag tattcggagg 5880
 attcagcctg caatggacag ttttcaaaag agaaaaattt aactaattgg aagccattta 5940
 atcaaaaaatt atgaatttag agattacttt gaaaaatgta tgattctaaa cgtttctttt 6000
 gtgtttattt gcaaaattca aatataagtt tttccacttt tcaaaaccta tttataaaaa 6060
 ttagaaaatt aaacaatttt ccaacaaca ttttttcccg tactgcatta aagtaacaac 6120
 ataaattgga agattagtaa ctactttggt catagtgttt ccaacaaagt gtgggttttta 6180
 tgatgctcac aataaatttt tcgaatgccg gttgaaacat ttttgaaaaa ttataaaaca 6240
 cgaaatgaat attttgcagt tgatagttac aaatccctgc caaatctttt ttttcacaaa 6300
 cttgaatttt aagaaatttg ctaaaaaaaa acttcggctg tttcatacat gccatataat 6360
 ttgtaaaaaa aaagtgaaaa tcgattcgtc gtgtgtagtt tcgccactca ctataaaatt 6420
 gctgattaag tatagtgagt ggcgaaactc ggaaattgtc ggccgccgtg gaaacctacc 6480
 ccaaaaccgg acgcagtgcg tccggtggtg ttaaaatcgg acgaccggac gccgatttgt 6540
 acagccctat ttgaaagtaa tgacgtcata cttactttca tacagaaatt aaatatctga 6600
 tacgttagat tttgggaaat aagcttgtca caaaaaatga tgtgggtttat ttctagaagt 6660
 cttactatgt agttggtaca caaaatatga aatttgtagc gtatgcttca tagcagttac 6720
 aaagtcgaga actatttgta cattaatttg accaacaac ttaccataaa ccagcacaat 6780
 caagaacaca gcgtatccac caacttccat aaacgaacgg gcagtcagct tgatctttcc 6840
 atccgatttc tcgtgtccgg atgccagcaa ggcttgagaa aacgagattc cctctttttg 6900
 agccggattc ttcttcttat cgtgctcata ctctcactg accatagaat ggtcaaacga 6960
 ggggccatgc tccgcagcgg cgaccggctg cgggtggatta gcccatcgct cgtccgcagc 7020
 gccgtagttc attgaagacg gctcgctgaa acagtagaaa atttgaatta aagttttgag 7080
 aaaagttgaa aatcgagagc tctgtagtgt aaaaactgga aaaatagagt cgaaaagagg 7140
 cgagctcgcg aaatccacgt cctcgtagct cttggagatg ccgcattgct aagagatttc 7200
 cgtagatact atgttttatg ggatttcacg tttttggttg gagacggttt tttgcataga 7260

```

aacggaaaaa tgatgcagga atagaaaacg aacatgattt gaaactgaaa accatcgact 7320
atacggcaca atcatactac atttatcggg ttattgaaac tgcaccccaa aagttttacaa 7380
tttaaattca cataccatctt gaagataaca acgaataaaa agacttcgaa aggcggcaaa 7440
tgtcgtgggtt tcgtgggtgta gtgggttatca catctgtcta acacacagaa ggtcgggtggt 7500
tcgagcccg ccgagatcat aagttttttg tcaatcatta atattgattc atctgaatga 7560
aattgtaaaa ttctttgaag gtgtttctaaa atattgaact gttttttttt agatttcggt 7620
agtatataat ttttgaaaca tacatctttt tcttccaaat ttcaagtatc ttctacgatt 7680
tttgaaaaat cccaaaaaatt gtaaacatta aaattctgaa taaacgggtg aaatttgtag 7740
ttctctcaaa ttctaaataa aaattgaacg aaatttgaga aatttcctgt ttcaaaaact 7800
aaatgtctta ttttcagagt tcaacaatgc cttagagaaa gttggaaaat gataatgttt 7860
gttagtatat tgagaatatc atgcaagtga aacaattagt ttttttttcg ataacaatta 7920
tttaaaaaaa actactgttt caaatctttt attcaaccaa tcctgtaata aaagttcact 7980
tatctttctc ctcttcatcc ataatgtatg cccctcttca aatggaaaat atgatgtcgg 8040
ggggagggtcc tccccctccc caccacctc cat 8073

```

```

<210> 6
<211> 815
<212> PRT
<213> C. Elegans Pkd-2 protein

```

```

<400> 6
Met Glu Gly Arg Gly Glu Gly Glu Asp Leu Pro Pro Thr Ser Tyr Phe
 1          5          10          15
Pro Phe Glu Glu Gly His Thr Leu Trp Met Lys Arg Glu Lys Ile Lys
          20          25          30
His Leu Gln Arg Ile Leu Gln Phe His Ser Asp Glu Ser Ile Leu Met
          35          40          45
Ile Asp Lys Lys Leu Met Ile Ser Gly Gly Leu Glu Pro Pro Thr Phe
          50          55          60
Cys Val Leu Asp Arg Cys Asp Asn His Tyr Thr Thr Lys Pro Arg His
          65          70          75          80
Leu Pro Pro Phe Glu Val Phe Leu Phe Val Val Ile Phe Lys Cys Glu
          85          90          95
Pro Ser Ser Met Asn Tyr Gly Ala Ala Asp Glu Arg Trp Ala Asn Pro
          100          105          110
Pro Gln Pro Val Ala Ala Ala Glu His Gly Pro Ser Phe Asp His Ser
          115          120          125
Met Val Ser Glu Glu Tyr Glu His Asp Lys Lys Lys Asn Pro Ala Gln
          130          135          140
Lys Glu Gly Ile Ser Phe Ser Gln Ala Leu Leu Ala Ser Gly His Glu
          145          150          155          160

```

Lys Ser Asp Gly Lys Ile Lys Leu Thr Ala Arg Ser Phe Met Glu Val
 165 170 175
 Gly Gly Tyr Ala Val Phe Leu Ile Val Leu Val Tyr Val Ala Phe Ala
 180 185 190
 Gln Asn Ser Ile Gln Ser Tyr Tyr Tyr Ser Lys Val Met Ser Asp Leu
 195 200 205
 Phe Val Ala Ser Thr Gly Ala Ser Gly Ala Pro Ala Phe Gly Ser Cys
 210 215 220
 Thr Ser Met Asp Asn Ile Trp Asp Trp Leu Ser Gln Val Leu Ile Pro
 225 230 235 240
 Gly Ile Tyr Trp Thr Glu Thr Ser Asn Ser Thr Asp Asn Glu Asn Met
 245 250 255
 Ile Tyr Tyr Glu Asn Arg Leu Leu Gly Glu Pro Arg Ile Arg Met Leu
 260 265 270
 Lys Val Thr Asn Asp Ser Cys Thr Val Met Lys Ser Phe Gln Arg Glu
 275 280 285
 Ile Lys Glu Cys Phe Ala Asn Tyr Glu Glu Lys Leu Glu Asp Lys Thr
 290 295 300
 Met Val Gly Asp Gly Ser Val Asp Ala Phe Ile Tyr Ala Thr Ala Lys
 305 310 315 320
 Glu Leu Glu Asn Leu Lys Thr Val Gly Thr Ile Ala Ser Tyr Gly Gly
 325 330 335
 Gly Gly Phe Val Gln Arg Leu Pro Val Ala Gly Ser Thr Glu Ala Gln
 340 345 350
 Ser Ala Ile Ala Thr Leu Lys Ala Asn Arg Trp Ile Asp Arg Gly Ser
 355 360 365
 Arg Ala Ile Ile Val Asp Phe Ala Leu Tyr Asn Ala Asn Ile Asn Leu
 370 375 380
 Phe Cys Val Val Lys Leu Leu Phe Glu Leu Pro Ala Ser Gly Gly Val
 385 390 395 400
 Ile Thr Thr Pro Lys Leu Met Thr Tyr Asp Leu Leu Thr Tyr Gln Thr
 405 410 415
 Ser Gly Gly Thr Arg Met Met Ile Phe Glu Gly Ile Phe Cys Gly Phe
 420 425 430
 Ile Leu Tyr Phe Ile Phe Glu Glu Leu Phe Ala Ile Gly Arg His Arg
 435 440 445
 Leu His Tyr Leu Thr Gln Phe Trp Asn Leu Val Asp Val Val Leu Leu
 450 455 460
 Gly Phe Ser Val Ala Thr Ile Ile Leu Ser Val Asn Arg Thr Lys Thr
 465 470 475 480
 Gly Val Asn Arg Val Asn Ser Val Ile Glu Asn Gly Leu Thr Asn Ala
 485 490 495
 Pro Phe Asp Asp Val Thr Ser Ser Glu Asn Ser Tyr Leu Asn Ile Lys
 500 505 510
 Ala Cys Val Val Phe Val Ala Trp Val Lys Val Phe Lys Phe Ile Ser

515					520					525					
Val	Asn	Lys	Thr	Met	Ser	Gln	Leu	Ser	Ser	Thr	Leu	Thr	Arg	Ser	Ala
530						535					540				
Lys	Asp	Ile	Gly	Gly	Phe	Ala	Val	Met	Phe	Ala	Val	Phe	Phe	Phe	Ala
545					550					555					560
Phe	Ala	Gln	Phe	Gly	Tyr	Leu	Cys	Phe	Gly	Thr	Gln	Ile	Ala	Asp	Tyr
				565					570					575	
Ser	Asn	Leu	Tyr	Asn	Ser	Ala	Phe	Ala	Leu	Leu	Arg	Leu	Ile	Leu	Gly
			580					585					590		
Asp	Phe	Asn	Phe	Ser	Ala	Leu	Glu	Ser	Cys	Asn	Arg	Phe	Phe	Gly	Pro
		595					600					605			
Ala	Phe	Phe	Ile	Ala	Tyr	Val	Phe	Phe	Val	Ser	Phe	Ile	Leu	Leu	Asn
	610					615					620				
Met	Phe	Leu	Ala	Ile	Ile	Asn	Asp	Ser	Tyr	Val	Glu	Val	Lys	Ala	Glu
625					630					635					640
Leu	Ala	Arg	Lys	Lys	Asp	Gly	Glu	Gly	Ile	Leu	Asp	Trp	Phe	Met	Asn
				645					650					655	
Lys	Val	Arg	Gly	Leu	Thr	Lys	Arg	Gly	Lys	Arg	Pro	Asp	Ala	Pro	Gly
			660					665					670		
Glu	Asp	Ala	Thr	Tyr	Glu	Asp	Tyr	Lys	Leu	Met	Leu	Tyr	Arg	Ala	Gly
		675					680						685		
Tyr	Ala	Glu	Lys	Asp	Ile	Asn	Glu	Ala	Phe	Thr	Arg	Phe	Asn	Val	Thr
	690					695					700				
Ser	Met	Thr	Glu	His	Val	Pro	Glu	Lys	Val	Ala	Glu	Asp	Ile	Ala	Asp
	705				710					715					720
Glu	Val	Ala	Arg	Met	Thr	Glu	Gln	Lys	Arg	Asn	Tyr	Met	Glu	Asn	His
				725					730					735	
Arg	Asp	Tyr	Ala	Asn	Leu	Asn	Arg	Arg	Val	Asp	Gln	Met	Gln	Glu	Ser
			740					745					750		
Val	Phe	Ser	Ile	Val	Asp	Arg	Ile	Glu	Gly	Val	Asn	Ala	Thr	Leu	Gln
		755					760					765			
Thr	Ile	Glu	Lys	Gln	Arg	Val	Gln	Gln	Gln	Asp	Gly	Gly	Asn	Leu	Met
	770					775					780				
Asp	Leu	Ser	Ala	Leu	Leu	Thr	Asn	Gln	Val	Arg	Asn	Arg	Glu	Ser	Ala
785					790					795					800
Ala	Arg	Arg	Pro	Thr	Ile	Thr	Ser	Ile	Ala	Asp	Lys	Lys	Glu	Glu	
				805					810					815	

<210> 7

<211> 22

<212> DNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Outside primer for PCR screening of lov-1 genomic (sy582) deletion

<400> 7

ctctatttgt ggttcgttgg cg

22

<210> 8

<211> 22

<212> DNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Outside primer for PCR screening of
lov-1 genomic (sy582) deletion

<400> 8

gggagtttcc gttttcatgg gg

22

<210> 9

<211> 22

<212> DNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Nested primer for PCR screening of
lov-1 genomic (sy582) deletion

<400> 9

ctaggaccga tgcaacagcg ag

22

<210> 10

<211> 22

<212> DNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Nested primer for PCR screening of
lov-1 genomic (sy582) deletion

<400> 10

aacgctgatt gggtcaagtg tg

22

<210> 11

<211> 23

<212> DNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Outside primer for PCR screening of
pkd-2 genomic (sy606) deletion

<400> 11

cccctcgttt gaccattcta tgg

23

<210> 12

<211> 22

<212> DNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Outside primer for PCR screening of
pkd-2 genomic (sy606) deletion

<400> 12

acgtgatacct ctgtcgatcc ag

22

<210> 13
<211> 22
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Nested primer for PCR screening of
pkd-2 genomic (*sy606*) deletion

<400> 13
agatcaagct gactgcccgt tc

22

<210> 14
<211> 23
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Nested primer for PCR screening of
pkd-2 genomic (*sy606*) deletion

<400> 14
gatccagcga ttagccttta acg

23

<210> 15
<211> 2870
<212> PRT
<213> C. Elegans Lov-1 *sy582* deletion protein

<400> 15

Met	Val	Leu	Arg	Phe	Ser	Pro	Pro	Phe	Arg	Phe	Ser	Thr	Thr	Ser	Phe
1				5					10					15	
Phe	Ser	Cys	Cys	Leu	Phe	Cys	Ser	Glu	Phe	Ile	Phe	Val	Phe	Arg	Arg
		20						25					30		
Ile	Phe	Thr	Lys	Leu	Leu	Gln	Asp	Asn	Leu	Pro	Ala	His	Trp	Met	Lys
		35					40					45			
Lys	Ser	Asn	Phe	Phe	Val	Leu	Leu	Leu	Ala	Ile	Ser	Ala	Ile	Gln	
	50					55				60					
Ile	Asp	Gly	Leu	His	Tyr	Gln	Leu	Leu	Asp	Gly	Ile	Ala	Thr	Phe	Arg
	65				70					75					80
Leu	Asp	Asn	Asp	Asp	Thr	Thr	Ile	Gly	Gly	Val	Pro	Arg	Asn	Ser	Gln
			85						90					95	
Gly	Val	Val	Lys	Ile	Lys	Leu	Ser	Cys	Gly	Leu	Asn	Arg	Leu	Ser	Val
			100					105					110		
Glu	Asn	Lys	Val	Thr	Glu	Val	Ser	Ser	Leu	Glu	Leu	Ile	His	Asn	Cys
		115					120					125			
Ile	Gln	Thr	Glu	Thr	Arg	Leu	Val	Gly	Leu	Phe	Leu	Asn	Ser	Thr	Trp
	130					135						140			
Ile	Thr	Leu	Asn	Glu	Val	Asn	Asp	Asp	Asp	Glu	Ile	Ser	Ile	Ala	Val
145					150					155					160
Glu	Ala	Lys	Tyr	Glu	Val	Cys	Tyr	Asp	Asp	Gly	Ile	Asp	Arg	Cys	Asp

165								170				175			
Gly	Ser	Leu	Trp	Trp	Leu	Gln	Val	Gly	Gly	Asn	Glu	Met	Ala	Leu	Leu
			180					185					190		
Gly	Tyr	Arg	Glu	Lys	Cys	Glu	Ser	Gly	Glu	Ile	Asn	Glu	Glu	Tyr	Ala
		195					200					205			
Arg	Arg	Met	Cys	Lys	Arg	Pro	Tyr	Arg	Ser	Glu	Lys	Ser	Thr	Ala	Ile
	210					215					220				
Ser	Asp	Ser	Gln	Gly	Val	Tyr	Tyr	Asp	Gly	Gln	Val	Leu	Lys	Gly	Val
225					230					235					240
Arg	Ala	Lys	Gln	Phe	Ser	Met	Arg	Thr	Ser	Gly	Ser	Pro	Thr	Leu	Arg
				245					250					255	
Arg	Met	Lys	Arg	Asp	Ala	Gly	Asp	Asn	Thr	Cys	Asp	Tyr	Thr	Ile	Glu
			260				265					270			
Ser	Thr	Ser	Thr	Ser	Thr	Thr	Thr	Pro	Thr	Thr	Thr	Thr	Val	Thr	Ser
		275					280					285			
Thr	Val	Thr	Ser	Thr	Thr	Thr	Val	Pro	Thr	Ser	Thr	Ser	Thr	Val	Thr
	290						295					300			
Thr	Ala	Met	Ser	Thr	Ser	Thr	Ser	Thr	Pro	Ser	Thr	Ser	Thr	Thr	Ile
305					310					315					320
Glu	Ser	Thr	Ser	Thr	Thr	Phe	Thr	Ser	Thr	Ala	Ser	Thr	Ser	Thr	Ser
				325					330					335	
Ser	Thr	Ser	Thr	Thr	Gln	Gln	Ser	Ser	Ser	Thr	Ile	Thr	Ser	Ser	Pro
			340				345						350		
Ser	Ser	Thr	Thr	Leu	Ser	Thr	Ser	Ile	Pro	Thr	Thr	Thr	Thr	Pro	Glu
		355				360						365			
Ile	Thr	Ser	Thr	Leu	Ser	Ser	Leu	Pro	Asp	Asn	Ala	Ile	Cys	Ser	Tyr
	370					375					380				
Leu	Asp	Glu	Thr	Thr	Thr	Ser	Thr	Thr	Phe	Thr	Thr	Thr	Met	Leu	Thr
385					390				395						400
Ser	Thr	Thr	Thr	Glu	Glu	Pro	Ser	Thr	Ser	Thr	Thr	Thr	Thr	Glu	Val
				405			410							415	
Thr	Ser	Thr	Ser	Ser	Thr	Val	Thr	Thr	Thr	Glu	Pro	Thr	Thr	Thr	Leu
			420				425						430		
Thr	Thr	Ser	Thr	Ala	Ser	Thr	Ser	Thr	Thr	Glu	Pro	Ser	Thr	Ser	Thr
		435				440						445			
Val	Thr	Thr	Ser	Pro	Ser	Thr	Ser	Pro	Val	Thr	Ser	Thr	Val	Thr	Ser
	450					455					460				
Ser	Ser	Ser	Ser	Ser	Thr	Thr	Val	Thr	Thr	Pro	Thr	Ser	Thr	Glu	Ser
465					470					475					480
Thr	Ser	Thr	Ser	Pro	Ser	Ser	Thr	Val	Thr	Thr	Ser	Thr	Thr	Ala	Pro
				485					490					495	
Ser	Thr	Ser	Thr	Thr	Gly	Pro	Ser	Ser	Ser	Ser	Ser	Thr	Pro	Ser	Ser
			500				505						510		
Thr	Ala	Ser	Ser	Ser	Val	Ser	Ser	Thr	Ala	Ser	Ser	Thr	Gln	Ser	Ser

005060 : 09453300

515	520	525																	
Thr Ser Thr Gln Gln Ser Ser	Thr Thr Thr Lys Ser	Glu Thr Thr Thr																	
530	535	540																	
Ser Ser Asp Gly Thr Asn Pro Asp Phe Tyr Phe Val Glu Lys Ala Thr																			
545	550	555																	560
Thr Thr Phe Tyr Asp Ser Thr Ser Val Asn Leu Thr Leu Asn Ser Gly																			
	565	570																	575
Leu Gly Ile Ile Gly Tyr Gln Thr Ser Ile Glu Cys Thr Ser Pro Thr																			
	580	585																	
Ser Ser Asn Tyr Val Ser Thr Thr Lys Asp Gly Ala Cys Phe Thr Lys																			
	595	600																	
Ser Val Ser Met Pro Arg Leu Gly Gly Thr Tyr Pro Ala Ser Thr Phe																			
	610	615																	
Val Gly Pro Gly Asn Tyr Thr Phe Arg Ala Thr Met Thr Thr Asp Asp																			
	625	630																	640
Lys Lys Val Tyr Tyr Thr Tyr Ala Asn Val Tyr Ile Gln Glu Tyr Ser																			
	645	650																	655
Ser Thr Thr Ile Glu Ser Glu Ser Ser Thr Ser Ala Val Ala Ser Ser																			
	660	665																	
Thr Ser Ser Thr Pro Ser Thr Pro Ser Ser Thr Leu Ser Thr Ser Thr																			
	675	680																	
Val Thr Glu Pro Ser Ser Thr Arg Ser Ser Asp Ser Thr Thr Thr Ser																			
	690	695																	
Ala Gly Ser Thr Thr Thr Leu Gln Glu Ser Thr Thr Thr Ser Glu Glu																			
	705	710																	720
Ser Thr Thr Asp Ser Ser Thr Thr Thr Ile Ser Asp Thr Ser Thr Ser																			
	725	730																	735
Thr Ser Ser Pro Ser Ser Thr Thr Ala Asp Ser Thr Ser Thr Leu Ser																			
	740	745																	
Val Asp Gln Phe Asp Phe Ile Leu Asp Ser Gly Leu Ser Trp Asn Glu																			
	755	760																	
Thr Arg His Asn Glu Asp Ser Ile Asn Ile Val Pro Leu Pro Thr Asn																			
	770	775																	
Ala Ile Thr Pro Thr Glu Arg Ser Gln Thr Phe Glu Cys Arg Asn Val																			
	785	790																	800
Ser Thr Glu Pro Phe Leu Ile Ile Lys Glu Ser Thr Cys Leu Asn Tyr																			
	805	810																	815
Ser Asn Thr Val Leu Asn Ala Thr Tyr Ser Ser Asn Ile Pro Ile Gln																			
	820	825																	
Pro Ile Glu Thr Phe Leu Val Gly Ile Gly Thr Tyr Glu Phe Arg Ile																			
	835	840																	
Asn Met Thr Asp Leu Thr Thr Met Gln Val Val Ser His Ile Phe Thr																			
	850	855																	
Leu Asn Val Val Ala Asp Ser Thr Ser Thr Ser Glu Val Thr Ser Thr																			

865		870		875		880
Thr Ser Thr Gly Ser	Ser Ser Ser Glu Ser Ser	Ala Ile Ser Thr Thr	Ser			
	885		890			
Gly Ile Glu Ser Thr	Ser Thr Leu Glu Ala Ser Thr Thr	Asp Ala Ser				
	900	905	910			
Gln Asp Ser Ser Thr	Ser Thr Ser Asp Ser Gly Thr Thr	Ser Asp Ser				
	915	920	925			
Thr Thr Ile Asp Ser	Ser Asn Ser Thr Pro Ser Thr	Ser Asp Ser Ser				
	930	935	940			
Gly Leu Ser Gln Thr	Pro Ser Asp Ser Ser Ser	Ala Ser Asp Ser	Met			
945	950	955	960			
Arg Thr Thr Thr Val	Asp Pro Asp Ala Ser Thr Glu Thr Pro Tyr	Asp				
	965	970	975			
Phe Val Leu Glu Asn	Leu Thr Trp Asn Glu Thr Val Tyr Tyr	Ser Glu				
	980	985	990			
Asn Pro Phe Tyr Ile	Thr Pro Ile Pro Asn Lys Glu Pro Gly	Ala Leu				
	995	1000	1005			
Thr Thr Ala Met Thr	Cys Gln Cys Arg Asn Asp Ser Ser	Gln Pro Phe				
1010	1015	1020				
Val Leu Leu Lys Glu	Ser Asn Cys Leu Thr Glu Phe Gly Lys	Asn Gly				
1025	1030	1035	1040			
Ala Tyr Ser Ala Ser	Val Ser Phe Asn Pro Met Thr Ser Phe	Val Pro				
	1045	1050	1055			
Ala Thr Gly Thr Tyr	Glu Phe Leu Ile Asn Val Thr Asn Arg	Ala Ser				
	1060	1065	1070			
Gly Glu Ser Ala Ser	His Ile Phe Thr Met Asn Val Val	Leu Pro Thr				
	1075	1080	1085			
Thr Thr Thr Glu Thr	Pro Pro Thr Thr Val Ser Ser Ser	Asp Asp Ala				
	1090	1095	1100			
Gly Gly Lys Thr Gly	Gly Thr Gly Ala Thr Gly Gly Thr Gly	Gly Thr				
1105	1110	1115	1120			
Gly Ser Gly Gly Ser	Ala Thr Thr Leu Ser Thr Gly Asp	Ala Val Arg				
	1125	1130	1135			
Ser Thr Thr Ser Gly	Ser Gly Ser Gly Gln Ser Ser Thr	Gly Ser Gly				
	1140	1145	1150			
Ala Gly Gly Ser Gly	Thr Thr Ala Ser Gly Ser Gly Ser	Gly Gly Ser				
	1155	1160	1165			
Ser Gly Thr Gly Ser	Asp Gly Val Asn Ser Gly Lys Thr Thr	Ala Leu				
	1170	1175	1180			
Asn Gly Asp Gly Thr	Gly Ser Gly Thr Ala Thr Thr Pro	Gly Ser His				
1185	1190	1195	1200			
Leu Gly Asp Gly Gly	Ser Thr Ser Gly Ser Gly Ser Asp	Ser Asn Gly				
	1205	1210	1215			
Ser Ser Gly Val Ser	Thr Lys Ser Ser Ser Gly Ser Asp	Thr Ser Gly				

1220	1225	1230
Ser Ser Asp Ser Ser Gly Ala Asn Gly Ala Phe Ser Ala Thr Ala Gln 1235 1240 1245		
Pro Ser Thr Arg Thr Thr Lys Thr Arg Ser Ser Leu Ala Thr Val Ser 1250 1255 1260		
Pro Ile Ser Ala Ala Glu Gln Ala Ile Ile Asp Ala Gln Lys Ala Asp 1265 1270 1275 1280		
Val Met Asn Gln Leu Ala Gly Ile Met Asp Gly Ser Ala Ser Asn Asn 1285 1290 1295		
Ser Leu Asn Thr Ser Ser Ser Leu Leu Asn Gln Ile Ser Ser Leu Pro 1300 1305 1310		
Ala Ala Asp Leu Val Glu Val Ala Gln Ser Leu Leu Ser Asn Thr Leu 1315 1320 1325		
Lys Ile Pro Gly Val Gly Asn Met Ser Ser Val Asp Val Leu Lys Thr 1330 1335 1340		
Leu Gln Asp Asn Ile Ala Thr Thr Asn Ser Glu Leu Ala Asp Glu Met 1345 1350 1355 1360		
Ala Lys Val Ile Thr Lys Leu Ala Asn Val Asn Met Thr Ser Ala Gln 1365 1370 1375		
Ser Leu Asn Ser Val Leu Ser Ser Leu Asp Leu Ala Leu Lys Gly Ser 1380 1385 1390		
Thr Val Tyr Thr Leu Gly Val Ser Ser Thr Lys Ser Lys Asp Gly Thr 1395 1400 1405		
Tyr Ala Val Ile Phe Gly Tyr Val Ile Ala Ser Gly Tyr Thr Leu Val 1410 1415 1420		
Ser Pro Arg Cys Thr Leu Ser Ile Tyr Gly Ser Thr Ile Tyr Leu Thr 1425 1430 1435 1440		
Gly Asp Thr Arg Ala Ser Tyr Lys Gln Leu Asp Gly Asp Thr Val Thr 1445 1450 1455		
Ala Asp Thr Met Leu Ala Ala Ala Ile Gly Ile Gln Gly Met Phe Ala 1460 1465 1470		
Thr Asn Gly Arg Thr Val Gln Val Glu Gln Asp Lys Ile Asp Asp Lys 1475 1480 1485		
Arg Ser Leu Val Ser Gly Asn Ile Met Ala Thr Met Ser Gly Val Gly 1490 1495 1500		
Asp Val Gln Ser Gly Glu Tyr Ser Tyr Asn Asp Met Tyr Val Thr Ala 1505 1510 1515 1520		
Trp Asn Val Thr Tyr Asp Asn Ser Thr Val Gly Ser Thr Ser Gln Lys 1525 1530 1535		
Asn Thr Ser Phe Ser Phe Asn Ile Pro Val Ser Glu Val Gln Tyr Ile 1540 1545 1550		
Leu Leu Ile Glu Ser Gly Thr Met Ile Lys Leu His Ser Thr Gln Asn 1555 1560 1565		
Ile Val Ser Arg Gly Leu Val Val Thr Ala Ser Tyr Gly Gly Val Thr 1570 1575 1580		

Tyr Thr Ile Thr Cys Thr Asn Gly Thr Gly Lys Phe Val Glu Val Asp
 1585 1590 1595 1600
 Thr Asp Asn Ala Ile Phe Ser Tyr Asn Ala Asp Ser Phe Thr Val Val
 1605 1610 1615
 Ala Ser Asp Gly Ser Ser Ala Ser Thr Val Lys Lys Leu Ile Gln Met
 1620 1625 1630
 Pro Ile Val Ile Glu Asn Val Asn Leu Ala Leu Phe Asn Gln Thr Thr
 1635 1640 1645
 Ser Pro Leu Val Phe Ser Asn Ala Gly Ser Tyr Ser Met Arg Met Val
 1650 1655 1660
 Leu Ser Pro Gln Asp Ile Gly Ile Pro Ala Val Ser Ala Leu Ser Gln
 1665 1670 1675 1680
 Thr Val Ser Ile Ser Thr Leu Ser Pro Thr Ala Ser Tyr Thr Lys Asp
 1685 1690 1695
 Asp Leu Gln Ser Leu Ile Lys Glu Gln Thr Leu Val Thr Val Ser Gly
 1700 1705 1710
 Thr Thr Ser Asn Ser Leu Leu Ser Ile Ala Gly Ser Leu Thr Ser Ala
 1715 1720 1725
 Leu Lys Ile Ala Leu Asp Asn Pro Leu Ser Ser Asp Leu Ala Ala Asn
 1730 1735 1740
 Leu Lys Tyr Ala Thr Asp Asn Tyr Asp Ser Leu Tyr Asn Val Leu Pro
 1745 1750 1755 1760
 Ser Asp Pro Asp Asn Ile Val Tyr Val Glu Glu Met Thr Ser Glu Glu
 1765 1770 1775
 Trp Ala Ala Tyr Val Thr Lys Met Phe Gln Lys Asn Ile Ala Lys Asn
 1780 1785 1790
 Leu Ala Asn Gln Leu Ala Ser Thr Leu Asp Thr Leu Glu Asn Thr Leu
 1795 1800 1805
 Ala Ala Arg Ala Ile Ala Thr Gly Asn Leu Pro Tyr Asp Tyr Ser Asn
 1810 1815 1820
 Ser Val Asp Gly Thr Gly Met Val Ile Val Ile Asp Asp Ala Ser Asn
 1825 1830 1835 1840
 Ile Val Gly Lys Thr Gln Asn Cys Glu Glu Trp Ala Phe Lys Leu Pro
 1845 1850 1855
 Ser Pro Ala Ser Thr Leu Asn Thr Ala Glu Ile Thr Asp Lys Thr Leu
 1860 1865 1870
 Ile Gln Val Gly Leu Val Cys Tyr Ala Thr Asn Pro Arg Thr Tyr Val
 1875 1880 1885
 Asp Asn Phe Asp Met Leu Ile Thr Ser Gly Ala Leu Glu Ala His Ile
 1890 1895 1900
 Lys Asp Glu Asn Gln Ile Ile Ile Pro Ile Thr Gly Thr Thr Ala Pro
 1905 1910 1915 1920
 Ile Tyr Val Asn Gly Arg Gly Ser Glu Asp Asp Ala Val Leu Thr Leu
 1925 1930 1935

Met	Gln	Gln	Gly	Asp	Phe	Ala	Ser	Tyr	Gln	Ile	Leu	Asp	Leu	His	Ala
1940				1945				1950							
Phe	Arg	Thr	Thr	Asn	Trp	Asn	Asn	Ser	Leu	Gln	Val	Glu	Ile	Ile	Ala
1955				1960				1965							
Ser	Gln	Asp	Tyr	Glu	Ile	Pro	Asn	Asn	Asp	Asp	Thr	Tyr	Met	Phe	Ser
1970				1975				1980							
Ser	Phe	Gln	Ser	Leu	Pro	Gly	Pro	Leu	Glu	Ser	Asn	His	Glu	Trp	Ile
1985				1990				1995				2000			
Phe	Asp	Leu	Asn	Thr	Leu	Asn	Lys	Thr	Ser	Asn	Tyr	Phe	Val	Thr	Ala
2005				2010				2015							
Gly	Asn	Leu	Ile	Asn	Asn	Thr	Gly	Leu	Phe	Phe	Ile	Gly	Ile	Gly	Lys
2020				2025				2030							
Arg	Asn	Ser	Ser	Thr	Asn	Thr	Gly	Asn	Ser	Ser	Asp	Ile	Val	Asn	Tyr
2035				2040				2045							
Gly	Gln	Tyr	Asp	Ser	Met	Gln	Trp	Ser	Phe	Ala	Arg	Ser	Val	Pro	Met
2050				2055				2060							
Asp	Tyr	Gln	Val	Ala	Ala	Val	Ser	Lys	Gly	Cys	Tyr	Phe	Tyr	Gln	Lys
2065				2070				2075				2080			
Thr	Ser	Asp	Val	Phe	Asn	Ser	Glu	Gly	Met	Tyr	Pro	Ser	Asp	Gly	Gln
2085				2090				2095							
Gly	Met	Gln	Phe	Val	Asn	Cys	Ser	Thr	Asp	His	Leu	Thr	Met	Phe	Ser
2100				2105				2110							
Val	Gly	Ala	Phe	Asn	Pro	Thr	Ile	Asp	Ala	Asp	Phe	Ser	Tyr	Asn	Tyr
2115				2120				2125							
Asn	Val	Asn	Glu	Ile	Glu	Lys	Asn	Val	Lys	Val	Met	Ile	Ala	Ala	Val
2130				2135				2140							
Phe	Met	Leu	Val	Val	Tyr	Gly	Cys	Leu	Thr	Ile	Asn	Ala	Ile	Ile	Cys
2145				2150				2155				2160			
Gln	Arg	Lys	Asp	Ala	Ser	Arg	Gly	Arg	Leu	Arg	Phe	Leu	Lys	Asp	Asn
2165				2170				2175							
Glu	Pro	His	Asp	Gly	Tyr	Met	Tyr	Val	Ile	Ala	Val	Glu	Thr	Gly	Tyr
2180				2185				2190							
Arg	Met	Phe	Ala	Thr	Thr	Asp	Ser	Thr	Ile	Cys	Phe	Asn	Leu	Ser	Gly
2195				2200				2205							
Asn	Glu	Gly	Asp	Gln	Ile	Phe	Arg	Ser	Phe	Arg	Ser	Glu	Glu	Asp	Gly
2210				2215				2220							
Asn	Trp	Glu	Phe	Pro	Phe	Ser	Trp	Gly	Thr	Thr	Asp	Arg	Phe	Val	Met
2225				2230				2235				2240			
Thr	Thr	Ala	Phe	Pro	Leu	Gly	Glu	Leu	Glu	Tyr	Met	Arg	Leu	Trp	Leu
2245				2250				2255							
Asp	Asp	Ala	Gly	Leu	Asp	His	Arg	Glu	Ser	Trp	Tyr	Cys	Asn	Arg	Ile
2260				2265				2270							
Ile	Val	Lys	Asp	Leu	Gln	Thr	Gln	Asp	Ile	Tyr	Tyr	Phe	Pro	Phe	Asn
2275				2280				2285							
Asn	Trp	Leu	Gly	Thr	Lys	Asn	Gly	Asp	Gly	Glu	Thr	Glu	Arg	Leu	Ala

2645

2650

2655

Arg Ile Gly Val Leu Ala Ala Thr Leu Asp Asn Ala Leu Gly Ala Ile
 2660 2665 2670
 Val Ser Phe Gly Ile Ala Phe Leu Phe Phe Ser Met Thr Phe Asn Ser
 2675 2680 2685
 Val Leu Tyr Ala Val Leu Gly Asn Lys Met Gly Gly Tyr Arg Ser Leu
 2690 2695 2700
 Met Ala Thr Phe Gln Thr Ala Leu Ala Gly Met Leu Gly Lys Leu Asp
 2705 2710 2715 2720
 Val Thr Ser Ile Gln Pro Ile Ser Gln Phe Ala Phe Val Val Ile Met
 2725 2730 2735
 Leu Tyr Met Ile Ala Gly Ser Lys Leu Val Leu Gln Leu Tyr Val Thr
 2740 2745 2750
 Ile Ile Met Phe Glu Phe Glu Glu Ile Arg Asn Asp Ser Glu Lys Gln
 2755 2760 2765
 Thr Asn Asp Tyr Glu Ile Ile Asp His Ile Lys Tyr Lys Thr Lys Arg
 2770 2775 2780
 Arg Leu Gly Leu Leu Glu Pro Lys Asp Phe Ala Pro Val Ser Ile Ala
 2785 2790 2795 2800
 Asp Thr Gln Lys Asp Phe Arg Leu Phe His Ser Ala Val Ala Lys Val
 2805 2810 2815
 Asn Leu Leu His His Arg Ala Thr Arg Met Leu Gln Thr Gln Gly Gln
 2820 2825 2830
 Tyr Gln Asn Gln Thr Val Ile Asn Tyr Thr Leu Ser Tyr Asp Pro Val
 2835 2840 2845
 Ser Ala Ile His Glu Thr Gly Pro Lys Arg Phe Gln Lys Trp Arg Leu
 2850 2855 2860
 Asn Asp Val Glu Lys Asp
 2865 2870

<210> 16

<211> 200

<212> PRT

<213> C. Elegans Pkd-2 deletion mutant (sy606) protein

<400> 16

Met Glu Gly Arg Gly Glu Gly Glu Asp Leu Pro Pro Thr Ser Tyr Phe
 1 5 10 15
 Pro Phe Glu Glu Gly His Thr Leu Trp Met Lys Arg Glu Lys Ile Lys
 20 25 30
 His Leu Gln Arg Ile Leu Gln Phe His Ser Asp Glu Ser Ile Leu Met
 35 40 45
 Ile Asp Lys Lys Leu Met Ile Ser Gly Gly Leu Glu Pro Pro Thr Phe
 50 55 60
 Cys Val Leu Asp Arg Cys Asp Asn His Tyr Thr Thr Lys Pro Arg His
 65 70 75 80

Leu	Pro	Pro	Phe	Glu	Val	Phe	Leu	Phe	Val	Val	Ile	Phe	Lys	Cys	Glu
				85					90					95	
Pro	Ser	Ser	Met	Asn	Tyr	Gly	Ala	Ala	Asp	Glu	Arg	Trp	Ala	Asn	Pro
			100					105					110		
Pro	Gln	Pro	Val	Ala	Ala	Ala	Glu	His	Gly	Pro	Ser	Phe	Asp	His	Ser
		115					120					125			
Met	Val	Ser	Glu	Glu	Tyr	Glu	His	Asp	Lys	Lys	Lys	Asn	Pro	Ala	Gln
	130					135					140				
Lys	Glu	Gly	Ile	Ser	Phe	Ser	Gln	Ala	Leu	Leu	Ala	Ser	Gly	His	Glu
145					150				155						160
Lys	Ser	Asp	Gly	Lys	Ile	Lys	Leu	Thr	Ala	Arg	Ser	Phe	Met	Glu	Val
				165					170					175	
Gly	Gly	Tyr	Ala	Val	Phe	Leu	Ile	Val	Leu	Val	Tyr	Asp	Ser	Ser	Thr
			180					185					190		
Pro	Arg	Gln	Lys	Ser	Leu	Lys	Thr								
		195				200									